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(54) Title: **NOVEL G PROTEIN-COUPLED RECEPTORS**

(57) Abstract: The present invention provides a gene encoding a G protein-coupled receptor termed nGPCR-x; constructs and recombinant host cells incorporating the genes; the nGPCR-x polypeptides encoded by the gene; antibodies to the nGPCR-x polypeptides; and methods of making and using all of the foregoing.



WO 01/83553 A2

NOVEL G PROTEIN-COUPLED RECEPTORS

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims priority to Application Serial Numbers 60/201,633 filed May 3, 2000, 60/201,632 filed May 3, 2000, 60/201,551 filed May 3, 2000, 60/201,549 filed May 3, 2000, 60/201,548 filed May 3, 2000, 60/201,552 filed May 3, 2000, 60/201,978 filed May 3, 2000, and 60/201,550 filed May 3, 2000, each of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates generally to the fields of genetics and cellular and molecular biology. More particularly, the invention relates to novel G protein coupled receptors, to polynucleotides that encode such novel receptors, to reagents such as antibodies, probes, primers and kits comprising such antibodies, probes, primers related to the same, and to methods which use the novel G protein coupled receptors, polynucleotides or reagents.

BACKGROUND OF THE INVENTION

The G protein-coupled receptors (GPCRs) form a vast superfamily of cell surface receptors which are characterized by an amino-terminal extracellular domain, a carboxyl-terminal intracellular domain, and a serpentine structure that passes through the cell membrane seven times. Hence, such receptors are sometimes also referred to as seven transmembrane (7TM) receptors. These seven transmembrane domains define three extracellular loops and three intracellular loops, in addition to the amino- and carboxy- terminal domains. The extracellular portions of the receptor have a role in recognizing and binding one or more extracellular binding partners (*e.g.*, ligands), whereas the intracellular portions have a role in recognizing and communicating with downstream molecules in the signal transduction cascade.

The G protein-coupled receptors bind a variety of ligands including calcium ions, hormones, chemokines, neuropeptides, neurotransmitters, nucleotides, lipids, odorants, and even photons, and are important in the normal (and sometimes the aberrant) function of many cell types. (See generally Strosberg, *Eur. J. Biochem.* 196:1-10 (1991) and Bohm *et al.*, *Biochem J.* 322:1-18 (1997)). When a specific ligand binds to its corresponding receptor, the ligand typically stimulates the receptor to activate a specific heterotrimeric guanine-nucleotide-binding regulatory protein (G-protein) that is coupled to the intracellular portion of the receptor. The G protein in turn transmits a signal to an effector molecule within the cell, by either stimulating or inhibiting the activity of that effector molecule. These effector molecules include adenylate cyclase, phospholipases and ion channels. Adenylate cyclase and phospholipases are enzymes

that are involved in the production of the second messenger molecules cAMP, inositol triphosphate and diacylglycerol. It is through this sequence of events that an extracellular ligand stimuli exerts intracellular changes through a G protein-coupled receptor. Each such receptor has its own characteristic primary structure, expression pattern, ligand-binding profile, and intracellular effector system.

Because of the vital role of G protein-coupled receptors in the communication between cells and their environment, such receptors are attractive targets for therapeutic intervention, for example by activating or antagonizing such receptors. For receptors having a known ligand, the identification of agonists or antagonists may be sought specifically to enhance or inhibit the action of the ligand. Some G protein-coupled receptors have roles in disease pathogenesis (*e.g.*, certain chemokine receptors that act as HIV co-receptors may have a role in AIDS pathogenesis), and are attractive targets for therapeutic intervention even in the absence of knowledge of the natural ligand of the receptor. Other receptors are attractive targets for therapeutic intervention by virtue of their expression pattern in tissues or cell types that are themselves attractive targets for therapeutic intervention. Examples of this latter category of receptors include receptors expressed in immune cells, which can be targeted to either inhibit autoimmune responses or to enhance immune responses to fight pathogens or cancer; and receptors expressed in the brain or other neural organs and tissues, which are likely targets in the treatment of mental disorder, depression, schizophrenia, bipolar disease, or other neurological disorders. This latter category of receptor is also useful as a marker for identifying and/or purifying (*e.g.*, via fluorescence-activated cell sorting) cellular subtypes that express the receptor. Unfortunately, only a limited number of G protein receptors from the central nervous system (CNS) are known. Thus, a need exists for G protein-coupled receptors that have been identified and show promise as targets for therapeutic intervention in a variety of animals, including humans.

SUMMARY OF THE INVENTION

The present invention relates to an isolated nucleic acid molecule that comprises a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence homologous to sequences selected from the group consisting of SEQ ID NO:68 to SEQ ID NO:136, or a fragment thereof. In some embodiments, the nucleic acid molecule comprises a sequence that encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO:68 to SEQ ID NO:136, or a fragment thereof. In some embodiments, the nucleic acid molecule comprises a sequence homologous to a sequence selected from the group consisting of

SEQ ID NO:1 to SEQ ID NO:67, or a fragment thereof. In some embodiments, the nucleic acid molecule comprises a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:67, or fragments thereof.

5 According to some embodiments, the present invention provides vectors which comprise the nucleic acid molecule of the invention. In some embodiments, the vector is an expression vector.

According to some embodiments, the present invention provides host cells which comprise the vectors of the invention. In some embodiments, the host cells comprise expression vectors.

10 The present invention provides an isolated nucleic acid molecule comprising a nucleotide sequence complementary to at least a portion of a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:67, said portion comprising at least 10 nucleotides.

The present invention provides a method of producing a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO:68 to SEQ ID NO:136, or a
15 homolog or fragment thereof. The method comprising the steps of introducing a recombinant expression vector that includes a nucleotide sequence that encodes the polypeptide into a compatible host cell, growing the host cell under conditions for expression of the polypeptide and recovering the polypeptide.

The present invention provides an isolated antibody which binds to an epitope on a
20 polypeptide comprising a sequence selected from the group consisting of SEQ ID NO:68 to SEQ ID NO:136, or a homolog or fragment thereof.

The present invention provides a method of inducing an immune response in a mammal against a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO:68 to SEQ ID NO:136, or a homolog or fragment thereof. The method comprises
25 administering to a mammal an amount of the polypeptide sufficient to induce said immune response.

The present invention provides a method for identifying a compound which binds nGPCR-x. The method comprises the steps of contacting nGPCR-x with a compound and determining whether the compound binds nGPCR-x.

30 The present invention provides a method for identifying a compound which binds a nucleic acid molecule encoding nGPCR-x. The method comprises the steps of contacting said nucleic acid molecule encoding nGPCR-x with a compound and determining whether said compound binds said nucleic acid molecule.

The present invention provides a method for identifying a compound which modulates the activity of nGPCR-x. The method comprises the steps of contacting nGPCR-x with a compound and determining whether nGPCR-x activity has been modulated.

The present invention provides a method of identifying an animal homolog of nGPCR-x.

5 The method comprises the steps screening a nucleic acid database of the animal with a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:67, or a portion thereof and determining whether a portion of said library or database is homologous to said sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:67, or portion thereof.

The present invention provides a method of identifying an animal homolog of nGPCR-x.

10 The methods comprises the steps screening a nucleic acid library of the animal with a nucleic acid molecule having a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:67, or a portion thereof and determining whether a portion of said library or database is homologous to said sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:67, or a portion thereof.

15 Another aspect of the present invention relates to methods of screening a human subject to diagnose a disorder affecting the brain or genetic predisposition therefor. The methods comprise the steps of assaying nucleic acid of a human subject to determine a presence or an absence of a mutation altering an amino acid sequence, expression, or biological activity of at least one nGPCR that is expressed in the brain. A diagnosis of the disorder or predisposition is
20 made from the presence or absence of the mutation. The presence of a mutation altering the amino acid sequence, expression, or biological activity of the nGPCR in the nucleic acid correlates with an increased risk of developing the disorder.

The present invention provides kits for screening a human subject to diagnose mental disorder or a genetic predisposition therefor. The kits include an oligonucleotide useful as a
25 probe for identifying polymorphisms in a human nGPCR-x. The oligonucleotide comprises 6-50 nucleotides in a sequence that is identical or complementary to a sequence of a wild type human nGPCR-x gene sequence or nGPCR-x coding sequence, except for one sequence difference selected from the group consisting of a nucleotide addition, a nucleotide deletion, or nucleotide substitution. The kit also includes a media packaged with the oligonucleotide. The media
30 contains information for identifying polymorphisms that correlate with mental disorder or a genetic predisposition therefor, the polymorphisms being identifiable using the oligonucleotide as a probe.

The present invention further relates to methods of identifying nGPCR allelic variants that correlates with mental disorders. The methods comprise the steps of providing biological samples that comprise nucleic acid from a human patient diagnosed with a mental disorder, or from the patient's genetic progenitors or progeny, and detecting in the nucleic acid the presence of one or more mutations in an nGPCR that is expressed in the brain. The nucleic acid includes sequences corresponding to the gene or genes encoding nGPCR. The one or more mutations detected indicate an allelic variant that correlates with a mental disorder.

The present invention further relates to purified polynucleotides comprising nucleotide sequences encoding alleles of nGPCR-x from a human with mental disorder. The polynucleotide hybridizes to the complement of nGPCR-x under the following hybridization conditions: (a) hybridization for 16 hours at 42C in a hybridization solution comprising 50% formamide, 1% SDS, 1 M NaCl, 10% dextran sulfate and (b) washing 2 times for 30 minutes at 60C in a wash solution comprising 0.1x SSC and 1% SDS.

The present invention also provides methods for identifying a modulator of biological activity of nGPCR-x comprising the steps of contacting a cell that expresses nGPCR-x in the presence and in the absence of a putative modulator compound and measuring nGPCR-x biological activity in the cell. The decreased or increased nGPCR-x biological activity in the presence versus absence of the putative modulator is indicative of a modulator of biological activity.

The present invention further provides methods to identify compounds useful for the treatment of mental disorders. The methods comprise the steps of contacting a composition comprising nGPCR-x with a compound suspected of binding nGPCR-x. The binding between nGPCR-x and the compound suspected of binding nGPCR-x is detected. Compounds identified as binding nGPCR-x are candidate compounds useful for the treatment of mental disorder. Compounds identified as binding nGPCR-x, or other nGPCRs can be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate their activity.

The present invention further provides methods for identifying a compound useful as a modulator of binding between nGPCR-x and a binding partner of nGPCR-x. The methods comprise the steps of contacting the binding partner and a composition comprising nGPCR-x in the presence and in the absence of a putative modulator compound and detecting binding between the binding partner and nGPCR-x. Decreased or increased binding between the binding partner and nGPCR-x in the presence of the putative modulator, as compared to binding in the

absence of the putative modulator is indicative a modulator compound useful for the treatment of a related disease or disorder. Compounds identified as modulating binding between nGPCR-x, or other nGPCRs and an nGPCR-x binding partner can be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate their activity as modulators.

Another aspect of the present invention relates to methods of purifying a G protein from a sample containing a G protein. The methods comprise the steps of contacting the sample with an nGPCR for a time sufficient to allow the G protein to form a complex with the nGPCR, isolating the complex from remaining components of the sample, maintaining the complex under conditions which result in dissociation of the G protein from the nGPCR, and isolating said G protein from the nGPCR.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Definitions

Various definitions are made throughout this document. Most words have the meaning that would be attributed to those words by one skilled in the art. Words specifically defined either below or elsewhere in this document have the meaning provided in the context of the present invention as a whole and as are typically understood by those skilled in the art.

“Synthesized” as used herein and understood in the art, refers to polynucleotides produced by purely chemical, as opposed to enzymatic, methods. “Wholly” synthesized DNA sequences are therefore produced entirely by chemical means, and “partially” synthesized DNAs embrace those wherein only portions of the resulting DNA were produced by chemical means.

By the term “region” is meant a physically contiguous portion of the primary structure of a biomolecule. In the case of proteins, a region is defined by a contiguous portion of the amino acid sequence of that protein.

The term “domain” is herein defined as referring to a structural part of a biomolecule that contributes to a known or suspected function of the biomolecule. Domains may be co-extensive with regions or portions thereof; domains may also incorporate a portion of a biomolecule that is distinct from a particular region, in addition to all or part of that region. Examples of GPCR protein domains include, but are not limited to, the extracellular (*i.e.*, N-terminal), transmembrane and cytoplasmic (*i.e.*, C-terminal) domains, which are co-extensive with like-named regions of GPCRs; each of the seven transmembrane segments of a GPCR; and each of the loop segments (both extracellular and intracellular loops) connecting adjacent transmembrane segments.

As used herein, the term “activity” refers to a variety of measurable indicia suggesting or revealing binding, either direct or indirect; affecting a response, i.e. having a measurable affect in response to some exposure or stimulus, including, for example, the affinity of a compound for directly binding a polypeptide or polynucleotide of the invention, or, for example, measurement of amounts of upstream or downstream proteins or other similar functions after some stimulus or event.

Unless indicated otherwise, as used herein, the abbreviation in lower case (gpcr) refers to a gene, cDNA, RNA or nucleic acid sequence, while the upper case version (GPCR) refers to a protein, polypeptide, peptide, oligopeptide, or amino acid sequence. The term “nGPCR-x” refers to any of the nGPCRs taught herein, while specific reference to a nGPCR (for example nGPCR-2653) refers only to that specific nGPCR.

As used herein, the term “antibody” is meant to refer to complete, intact antibodies, and Fab, Fab’, F(ab)2, and other fragments thereof. Complete, intact antibodies include monoclonal antibodies such as murine monoclonal antibodies, chimeric antibodies and humanized antibodies.

As used herein, the term “binding” means the physical or chemical interaction between two proteins or compounds or associated proteins or compounds or combinations thereof. Binding includes ionic, non-ionic, Hydrogen bonds, Van der Waals, hydrophobic interactions, etc. The physical interaction, the binding, can be either direct or indirect, indirect being through or due to the effects of another protein or compound. Direct binding refers to interactions that do not take place through or due to the effect of another protein or compound but instead are without other substantial chemical intermediates. Binding may be detected in many different manners. As a non-limiting example, the physical binding interaction between a nGPCR-x of the invention and a compound can be detected using a labeled compound. Alternatively, functional evidence of binding can be detected using, for example, a cell transfected with and expressing a nGPCR-x of the invention. Binding of the transfected cell to a ligand of the nGPCR that was transfected into the cell provides functional evidence of binding. Other methods of detecting binding are well-known to those of skill in the art.

As used herein, the term “compound” means any identifiable chemical or molecule, including, but not limited to, small molecule, peptide, protein, sugar, nucleotide, or nucleic acid, and such compound can be natural or synthetic.

As used herein, the term “complementary” refers to Watson-Crick basepairing between nucleotide units of a nucleic acid molecule.

As used herein, the term "contacting" means bringing together, either directly or indirectly, a compound into physical proximity to a polypeptide or polynucleotide of the invention. The polypeptide or polynucleotide can be in any number of buffers, salts, solutions etc. Contacting includes, for example, placing the compound into a beaker, microtiter plate, cell culture flask, or a microarray, such as a gene chip, or the like, which contains the nucleic acid molecule, or polypeptide encoding the nGPCR or fragment thereof.

As used herein, the phrase "homologous nucleotide sequence," or "homologous amino acid sequence," or variations thereof, refers to sequences characterized by a homology, at the nucleotide level or amino acid level, of at least the specified percentage. Homologous nucleotide sequences include those sequences coding for isoforms of proteins. Such isoforms can be expressed in different tissues of the same organism as a result of, for example, alternative splicing of RNA. Alternatively, isoforms can be encoded by different genes. Homologous nucleotide sequences include nucleotide sequences encoding for a protein of a species other than humans, including, but not limited to, mammals. Homologous nucleotide sequences also include, but are not limited to, naturally occurring allelic variations and mutations of the nucleotide sequences set forth herein. A homologous nucleotide sequence does not, however, include the nucleotide sequence encoding other known GPCRs. Homologous amino acid sequences include those amino acid sequences which contain conservative amino acid substitutions and which polypeptides have the same binding and/or activity. A homologous amino acid sequence does not, however, include the amino acid sequence encoding other known GPCRs. Percent homology can be determined by, for example, the Gap program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, Madison WI), using the default settings, which uses the algorithm of Smith and Waterman (*Adv. Appl. Math.*, 1981, 2, 482-489, which is incorporated herein by reference in its entirety).

As used herein, the term "isolated" nucleic acid molecule refers to a nucleic acid molecule (DNA or RNA) that has been removed from its native environment. Examples of isolated nucleic acid molecules include, but are not limited to, recombinant DNA molecules contained in a vector, recombinant DNA molecules maintained in a heterologous host cell, partially or substantially purified nucleic acid molecules, and synthetic DNA or RNA molecules.

As used herein, the terms "modulates" or "modifies" means an increase or decrease in the amount, quality, or effect of a particular activity or protein.

As used herein, the term "oligonucleotide" refers to a series of linked nucleotide residues which has a sufficient number of bases to be used in a polymerase chain reaction (PCR). This short sequence is based on (or designed from) a genomic or cDNA sequence and is used to amplify, confirm, or reveal the presence of an identical, similar or complementary DNA or RNA in a particular cell or tissue. Oligonucleotides comprise portions of a DNA sequence having at least about 10 nucleotides and as many as about 50 nucleotides, preferably about 15 to 30 nucleotides. They are chemically synthesized and may be used as probes.

As used herein, the term "probe" refers to nucleic acid sequences of variable length, preferably between at least about 10 and as many as about 6,000 nucleotides, depending on use. They are used in the detection of identical, similar, or complementary nucleic acid sequences. Longer length probes are usually obtained from a natural or recombinant source, are highly specific and much slower to hybridize than oligomers. They may be single- or double-stranded and carefully designed to have specificity in PCR, hybridization membrane-based, or ELISA-like technologies.

The term "preventing" refers to decreasing the probability that an organism contracts or develops an abnormal condition.

The term "treating" refers to having a therapeutic effect and at least partially alleviating or abrogating an abnormal condition in the organism.

The term "therapeutic effect" refers to the inhibition or activation factors causing or contributing to the abnormal condition. A therapeutic effect relieves to some extent one or more of the symptoms of the abnormal condition. In reference to the treatment of abnormal conditions, a therapeutic effect can refer to one or more of the following: (a) an increase in the proliferation, growth, and/or differentiation of cells; (b) inhibition (*i.e.*, slowing or stopping) of cell death; (c) inhibition of degeneration; (d) relieving to some extent one or more of the symptoms associated with the abnormal condition; and (e) enhancing the function of the affected population of cells. Compounds demonstrating efficacy against abnormal conditions can be identified as described herein.

The term "abnormal condition" refers to a function in the cells or tissues of an organism that deviates from their normal functions in that organism. An abnormal condition can relate to cell proliferation, cell differentiation, cell signaling, or cell survival. An abnormal condition may also include obesity, diabetic complications such as retinal degeneration, and irregularities in glucose uptake and metabolism, and fatty acid uptake and metabolism.

Abnormal cell proliferative conditions include cancers such as fibrotic and mesangial disorders, abnormal angiogenesis and vasculogenesis, wound healing, psoriasis, diabetes mellitus, and inflammation.

Abnormal differentiation conditions include, but are not limited to, neurodegenerative disorders, slow wound healing rates, and slow tissue grafting healing rates. Abnormal cell signaling conditions include, but are not limited to, psychiatric disorders involving excess neurotransmitter activity.

Abnormal cell survival conditions may also relate to conditions in which programmed cell death (apoptosis) pathways are activated or abrogated. A number of protein kinases are associated with the apoptosis pathways. Aberrations in the function of any one of the protein kinases could lead to cell immortality or premature cell death.

The term "administering" relates to a method of incorporating a compound into cells or tissues of an organism. The abnormal condition can be prevented or treated when the cells or tissues of the organism exist within the organism or outside of the organism. Cells existing outside the organism can be maintained or grown in cell culture dishes. For cells harbored within the organism, many techniques exist in the art to administer compounds, including (but not limited to) oral, parenteral, dermal, injection, and aerosol applications. For cells outside of the organism, multiple techniques exist in the art to administer the compounds, including (but not limited to) cell microinjection techniques, transformation techniques and carrier techniques.

The abnormal condition can also be prevented or treated by administering a compound to a group of cells having an aberration in a signal transduction pathway to an organism. The effect of administering a compound on organism function can then be monitored. The organism is preferably a mouse, rat, rabbit, guinea pig or goat, more preferably a monkey or ape, and most preferably a human.

By "amplification" it is meant increased numbers of DNA or RNA in a cell compared with normal cells. "Amplification" as it refers to RNA can be the detectable presence of RNA in cells, since in some normal cells there is no basal expression of RNA. In other normal cells, a basal level of expression exists, therefore in these cases amplification is the detection of at least 1 to 2-fold, and preferably more, compared to the basal level.

As used herein, the phrase "stringent hybridization conditions" or "stringent conditions" refers to conditions under which a probe, primer, or oligonucleotide will hybridize to its target sequence, but to no other sequences. Stringent conditions are sequence-dependent and will be different in different circumstances. Longer sequences hybridize specifically at higher

temperatures. Generally, stringent conditions are selected to be about 5C lower than the thermal melting point (T_m) for the specific sequence at a defined ionic strength and pH. The T_m is the temperature (under defined ionic strength, pH and nucleic acid concentration) at which 50% of the probes complementary to the target sequence hybridize to the target sequence at equilibrium.

- 5 Since the target sequences are generally present in excess, at T_m , 50% of the probes are occupied at equilibrium. Typically, stringent conditions will be those in which the salt concentration is less than about 1.0 M sodium ion, typically about 0.01 to 1.0 M sodium ion (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30C for short probes, primers or oligonucleotides (e.g. 10 to 50 nucleotides) and at least about 60C for longer probes, primers or oligonucleotides.
- 10 Stringent conditions may also be achieved with the addition of destabilizing agents, such as formamide.

The amino acid sequences are presented in the amino to carboxy direction, from left to right. The amino and carboxy groups are not presented in the sequence. The nucleotide sequences are presented by single strand only, in the 5' to 3' direction, from left to right.

- 15 Nucleotides and amino acids are represented in the manner recommended by the IUPAC-IUB Biochemical Nomenclature Commission or (for amino acids) by three letters code.

Polynucleotides

- The present invention provides purified and isolated polynucleotides (*e.g.*, DNA sequences and RNA transcripts, both sense and complementary antisense strands, both single- and double-stranded, including splice variants thereof) that encode unknown G protein-coupled receptors heretofore termed novel GPCRs, or nGPCRs. These genes are described herein and designated herein collectively as nGPCR-x (where x is 1011, 1012, 1013, 1014, 1015, 1016, 1017, 1018, 1019, 1020, 1021, 1022, 1023, 1024, 1025, 1026, 1027, 1028, 1029, 1030, 1031, 1032, 1033, 1034, 1035, 1036, 1037, 1038, 1039, 1040, 1041, 1042, 1043, 1044, 1045, 1046, 1047, 1048, 1049, 1050, 1051, 1052, 1053, 1054, 1055, 1056, 1057, 1058, 1059, 1060, 1061, 1062, 1063, 1064, 1065, 1066, 1067, 1068, 1069, 1070, 1071, 1072, 1073, 1074, 1075, 1076, and 1077). That is, these genes are described herein and designated herein as nGPCR-1011, nGPCR-1012, etc. Table 1 below identifies the novel gene sequence nGPCR-x designation, the SEQ ID NO: of the gene sequence, the SEQ ID NO: of the polypeptide encoded thereby, and the
- 30 U.S. Provisional Application in which the gene sequence has been disclosed.

Table 1

nGPCR	Nucleotide Sequence (SEQ ID NO:)	Amino acid Sequence (SEQ ID NO:)	Originally filed in:
1011	1	68	A
1012	2	69	A

1013	3	70	A
1014	4	71	A
1015	5	72	A
1016	6	73	A
1017	7	74	A
1018	8	75	A
1019	9	76	A
1020	10	77	A
1021	11	78, 135	B
1022	12	79	B
1023	13	80	B
1024	14	81	B
1025	15	82	B
1026	16	83	C
1027	17	84	C
1028	18	85	C
1029	19	86	C
1030	20	87	C
1031	21	88	C
1032	22	89	C
1033	23	90	C
1034	24	91	C
1035	25	92	C
1036	26	93	D
1037	27	94	D
1038	28	95	D
1039	29	96	D
1040	30	97	D
1041	31	98	D
1042	32	99	D
1043	33	100	D
1044	34	101	D
1045	35	102	D
1046	36	103	E
1047	37	104	E
1048	38	105	E
1049	39	106	E
1050	40	107	F
1051	41	108	F
1052	42	109	F
1053	43	110	F
1054	44	111	F
1055	45	112	F
1056	46	113	F
1057	47	114	F
1058	48	115	F
1059	49	116	F
1060	50	117	G
1061	51	118	G
1062	52	119	G
1063	53	120	G
1064	54	121, 136	G
1065	55	122	G
1066	56	123	G
1067	57	124	G
1068	58	125	G
1069	59	126	G
1070	60	127	H
1071	61	128	H
1072	62	129	H
1073	63	130	H
1074	64	131	H
1075	65	132	H

1076	66	133	H
1077	67	134	H

Legend

A= Ser. No. 60/201,633

B= Ser. No. 60/201,632

C= Ser. No. 60/201,551

D= Ser. No. 60/201,549

E= Ser. No. 60/201,548

F= Ser. No. 60/201,552

G= Ser. No. 60/201,978

H= Ser. No. 60/201,550

When a specific nGPCR is identified (for example nGPCR-1011), it is understood that only that specific nGPCR is being referred to.

As one skilled in the art knows, numerous GPCRs have been discovered in the brain, indicating that these nGPCR proteins are neuroreceptors.

The invention provides purified and isolated polynucleotides (*e.g.*, cDNA, genomic DNA, synthetic DNA, RNA, or combinations thereof, whether single- or double-stranded) that comprise a nucleotide sequence encoding the amino acid sequence of the polypeptides of the invention. Such polynucleotides are useful for recombinantly expressing the receptor and also for detecting expression of the receptor in cells (*e.g.*, using Northern hybridization and *in situ* hybridization assays). Such polynucleotides also are useful in the design of antisense and other molecules for the suppression of the expression of nGPCR-x in a cultured cell, a tissue, or an animal; for therapeutic purposes; or to provide a model for diseases or conditions characterized by aberrant nGPCR-x expression. Specifically excluded from the definition of polynucleotides of the invention are entire isolated, non-recombinant native chromosomes of host cells. A preferred polynucleotide has a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:67, which correspond to naturally occurring nGPCR-x sequences. It will be appreciated that numerous other polynucleotide sequences exist that also encode nGPCR-x having the sequence selected from the group consisting of SEQ ID NO:68 to SEQ ID NO:136, due to the well-known degeneracy of the universal genetic code.

The invention also provides a purified and isolated polynucleotide comprising a nucleotide sequence that encodes a mammalian polypeptide, wherein the polynucleotide hybridizes to a polynucleotide having the sequence set forth in sequences selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:67, or the non-coding strand complementary thereto, under the following hybridization conditions: (a) hybridization for 16 hours at 42C in a hybridization solution comprising 50% formamide, 1% SDS, 1 M NaCl, 10% dextran sulfate; and (b) washing 2 times for 30 minutes each at 60C in a wash solution comprising 0.1% SSC, 1% SDS. Polynucleotides that encode a human allelic variant are highly preferred.

The present invention relates to molecules which comprise the gene sequences that encode the nGPCRs; constructs and recombinant host cells incorporating the gene sequences;

the novel GPCR polypeptides encoded by the gene sequences; antibodies to the polypeptides and homologs; kits employing the polynucleotides and polypeptides, and methods of making and using all of the foregoing. In addition, the present invention relates to homologs of the gene sequences and of the polypeptides and methods of making and using the same.

5 Genomic DNA of the invention comprises the protein-coding region for a polypeptide of the invention and is also intended to include allelic variants thereof. It is widely understood that, for many genes, genomic DNA is transcribed into RNA transcripts that undergo one or more splicing events wherein intron (*i.e.*, non-coding regions) of the transcripts are removed, or “spliced out.” RNA transcripts that can be spliced by alternative mechanisms, and therefore be
10 subject to removal of different RNA sequences but still encode a nGPCR-x polypeptide, are referred to in the art as splice variants which are embraced by the invention. Splice variants comprehended by the invention therefore are encoded by the same original genomic DNA sequences but arise from distinct mRNA transcripts. Allelic variants are modified forms of a wild-type gene sequence, the modification resulting from recombination during chromosomal
15 segregation or exposure to conditions which give rise to genetic mutation. Allelic variants, like wild type genes, are naturally occurring sequences (as opposed to non-naturally occurring variants that arise from *in vitro* manipulation).

 The invention also comprehends cDNA that is obtained through reverse transcription of an RNA polynucleotide encoding nGPCR-x (conventionally followed by second strand
20 synthesis of a complementary strand to provide a double-stranded DNA).

 Preferred DNA sequences encoding human nGPCR-x polypeptides are selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:67. A preferred DNA of the invention comprises a double stranded molecule along with the complementary molecule (the “non-coding strand” or “complement”) having a sequence unambiguously deducible from the coding strand
25 according to Watson-Crick base-pairing rules for DNA. Also preferred are other polynucleotides encoding the nGPCR-x polypeptide selected from the group consisting of SEQ ID NO:68 to SEQ ID NO:136, which differ in sequence from the polynucleotides selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:67, by virtue of the well-known degeneracy of the universal nuclear genetic code.

30 The invention further embraces other species, preferably mammalian, homologs of the human nGPCR-x DNA. Species homologs, sometimes referred to as “orthologs,” in general, share at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least

99% homology with human DNA of the invention. Generally, percent sequence "homology" with respect to polynucleotides of the invention may be calculated as the percentage of nucleotide bases in the candidate sequence that are identical to nucleotides in the nGPCR-x sequence set forth in sequences selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:67, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity.

Polynucleotides of the invention permit identification and isolation of polynucleotides encoding related nGPCR-x polypeptides, such as human allelic variants and species homologs, by well-known techniques including Southern and/or Northern hybridization, and polymerase chain reaction (PCR). Examples of related polynucleotides include human and non-human genomic sequences, including allelic variants, as well as polynucleotides encoding polypeptides homologous to nGPCR-x and structurally related polypeptides sharing one or more biological, immunological, and/or physical properties of nGPCR-x. Non-human species genes encoding proteins homologous to nGPCR-x can also be identified by Southern and/or PCR analysis and are useful in animal models for nGPCR-x disorders. Knowledge of the sequence of a human nGPCR-x DNA also makes possible through use of Southern hybridization or polymerase chain reaction (PCR) the identification of genomic DNA sequences encoding nGPCR-x expression control regulatory sequences such as promoters, operators, enhancers, repressors, and the like. Polynucleotides of the invention are also useful in hybridization assays to detect the capacity of cells to express nGPCR-x. Polynucleotides of the invention may also provide a basis for diagnostic methods useful for identifying a genetic alteration(s) in a nGPCR-x locus that underlies a disease state or states, which information is useful both for diagnosis and for selection of therapeutic strategies.

According to the present invention, the nGPCR-x nucleotide sequences disclosed herein may be used to identify homologs of the nGPCR-x, in other animals, including but not limited to humans and other mammals, and invertebrates. Any of the nucleotide sequences disclosed herein, or any portion thereof, can be used, for example, as probes to screen databases or nucleic acid libraries, such as, for example, genomic or cDNA libraries, to identify homologs, using screening procedures well known to those skilled in the art. Accordingly, homologs having at least 50%, more preferably at least 60%, more preferably at least 70%, more preferably at least 80%, more preferably at least 90 %, more preferably at least 95%, and most preferably at least 100% homology with nGPCR-x sequences can be identified.

The disclosure herein of full-length polynucleotides encoding nGPCR-x polypeptides makes readily available to the worker of ordinary skill in the art every possible fragment of the full-length polynucleotide.

One preferred embodiment of the present invention provides an isolated nucleic acid molecule comprising a sequence homologous sequences selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:67, and fragments thereof. Another preferred embodiment provides an isolated nucleic acid molecule comprising a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:67, and fragments thereof.

As used in the present invention, fragments of nGPCR-x-encoding polynucleotides comprise at least 10, and preferably at least 12, 14, 16, 18, 20, 25, 50, or 75 consecutive nucleotides of a polynucleotide encoding nGPCR-x. Preferably, fragment polynucleotides of the invention comprise sequences unique to the nGPCR-x-encoding polynucleotide sequence, and therefore hybridize under highly stringent or moderately stringent conditions only (*i.e.*, “specifically”) to polynucleotides encoding nGPCR-x (or fragments thereof). Polynucleotide fragments of genomic sequences of the invention comprise not only sequences unique to the coding region, but also include fragments of the full-length sequence derived from introns, regulatory regions, and/or other non-translated sequences. Sequences unique to polynucleotides of the invention are recognizable through sequence comparison to other known polynucleotides, and can be identified through use of alignment programs routinely utilized in the art, *e.g.*, those made available in public sequence databases. Such sequences also are recognizable from Southern hybridization analyses to determine the number of fragments of genomic DNA to which a polynucleotide will hybridize. Polynucleotides of the invention can be labeled in a manner that permits their detection, including radioactive, fluorescent, and enzymatic labeling.

Fragment polynucleotides are particularly useful as probes for detection of full-length or fragments of nGPCR-x polynucleotides. One or more polynucleotides can be included in kits that are used to detect the presence of a polynucleotide encoding nGPCR-x, or used to detect variations in a polynucleotide sequence encoding nGPCR-x.

The invention also embraces DNAs encoding nGPCR-x polypeptides that hybridize under moderately stringent or high stringency conditions to the non-coding strand, or complement, of the polynucleotides set forth in sequences selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:67.

Exemplary highly stringent hybridization conditions are as follows: hybridization at 42C in a hybridization solution comprising 50% formamide, 1% SDS, 1 M NaCl, 10% Dextran

sulfate, and washing twice for 30 minutes at 60C in a wash solution comprising 0.1 X SSC and 1% SDS. It is understood in the art that conditions of equivalent stringency can be achieved through variation of temperature and buffer, or salt concentration as described Ausubel *et al.* (Eds.), *Protocols in Molecular Biology*, John Wiley & Sons (1994), pp. 6.0.3 to 6.4.10.

5 Modifications in hybridization conditions can be empirically determined or precisely calculated based on the length and the percentage of guanosine/cytosine (GC) base pairing of the probe. The hybridization conditions can be calculated as described in Sambrook, *et al.*, (Eds.), *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press: Cold Spring Harbor, New York (1989), pp. 9.47 to 9.51.

10 With the knowledge of the nucleotide sequence information disclosed in the present invention, one skilled in the art can identify and obtain nucleotide sequences which encode nGPCR-x from different sources (*i.e.*, different tissues or different organisms) through a variety of means well known to the skilled artisan and as disclosed by, for example, Sambrook *et al.*, "Molecular cloning: a laboratory manual", Second Edition, Cold Spring Harbor Press, Cold
15 Spring Harbor, NY (1989), which is incorporated herein by reference in its entirety.

For example, DNA that encodes nGPCR-x may be obtained by screening of mRNA, cDNA, or genomic DNA with oligonucleotide probes generated from the nGPCR-x gene sequence information provided herein. Probes may be labeled with a detectable group, such as a fluorescent group, a radioactive atom or a chemiluminescent group in accordance with
20 procedures known to the skilled artisan and used in conventional hybridization assays, as described by, for example, Sambrook *et al.*

A nucleic acid molecule comprising any of the nGPCR-x nucleotide sequences described above can alternatively be synthesized by use of the polymerase chain reaction (PCR) procedure, with the PCR oligonucleotide primers produced from the nucleotide sequences
25 provided herein. See U.S. Patent Numbers 4,683,195 to Mullis *et al.* and 4,683,202 to Mullis. The PCR reaction provides a method for selectively increasing the concentration of a particular nucleic acid sequence even when that sequence has not been previously purified and is present only in a single copy in a particular sample. The method can be used to amplify either single- or double-stranded DNA. The essence of the method involves the use of two oligonucleotide
30 probes to serve as primers for the template-dependent, polymerase mediated replication of a desired nucleic acid molecule.

A wide variety of alternative cloning and *in vitro* amplification methodologies are well known to those skilled in the art. Examples of these techniques are found in, for example,

Berger *et al.*, *Guide to Molecular Cloning Techniques*, Methods in Enzymology 152, Academic Press, Inc., San Diego, CA (Berger), which is incorporated herein by reference in its entirety.

Automated sequencing methods can be used to obtain or verify the nucleotide sequence of nGPCR-x. The nGPCR-x nucleotide sequences of the present invention are believed to be 5 100% accurate. However, as is known in the art, nucleotide sequence obtained by automated methods may contain some errors. Nucleotide sequences determined by automation are typically at least about 90%, more typically at least about 95% to at least about 99.9% identical to the actual nucleotide sequence of a given nucleic acid molecule. The actual sequence may be more precisely determined using manual sequencing methods, which are well known in the art. An 10 error in a sequence which results in an insertion or deletion of one or more nucleotides may result in a frame shift in translation such that the predicted amino acid sequence will differ from that which would be predicted from the actual nucleotide sequence of the nucleic acid molecule, starting at the point of the mutation.

The nucleic acid molecules of the present invention, and fragments derived therefrom, 15 are useful for screening for restriction fragment length polymorphism (RFLP) associated with certain disorders, as well as for genetic mapping.

The polynucleotide sequence information provided by the invention makes possible large-scale expression of the encoded polypeptide by techniques well known and routinely practiced in the art.

20 Vectors

Another aspect of the present invention is directed to vectors, or recombinant expression vectors, comprising any of the nucleic acid molecules described above. Vectors are used herein either to amplify DNA or RNA encoding nGPCR-x and/or to express DNA which encodes nGPCR-x. Preferred vectors include, but are not limited to, plasmids, phages, cosmids, 25 episomes, viral particles or viruses, and integratable DNA fragments (*i.e.*, fragments integratable into the host genome by homologous recombination). Preferred viral particles include, but are not limited to, adenoviruses, baculoviruses, parvoviruses, herpesviruses, poxviruses, adeno-associated viruses, Semliki Forest viruses, vaccinia viruses, and retroviruses. Preferred expression vectors include, but are not limited to, pcDNA3 (Invitrogen) and pSVL (Pharmacia Biotech). Other expression vectors include, but are not limited to, pSPORT™ vectors, pGEM™ 30 vectors (Promega), pPROEXvectors™ (LTI, Bethesda, MD), Bluescript™ vectors (Stratagene), pQE™ vectors (Qiagen), pSE420™ (Invitrogen), and pYES2™ (Invitrogen).

Expression constructs preferably comprise GPCR-x-encoding polynucleotides operatively linked to an endogenous or exogenous expression control DNA sequence and a transcription terminator. Expression control DNA sequences include promoters, enhancers, operators, and regulatory element binding sites generally, and are typically selected based on the expression systems in which the expression construct is to be utilized. Preferred promoter and enhancer sequences are generally selected for the ability to increase gene expression, while operator sequences are generally selected for the ability to regulate gene expression. Expression constructs of the invention may also include sequences encoding one or more selectable markers that permit identification of host cells bearing the construct. Expression constructs may also include sequences that facilitate, and preferably promote, homologous recombination in a host cell. Preferred constructs of the invention also include sequences necessary for replication in a host cell.

Expression constructs are preferably utilized for production of an encoded protein, but may also be utilized simply to amplify a nGPCR-x-encoding polynucleotide sequence. In preferred embodiments, the vector is an expression vector wherein the polynucleotide of the invention is operatively linked to a polynucleotide comprising an expression control sequence. Autonomously replicating recombinant expression constructs such as plasmid and viral DNA vectors incorporating polynucleotides of the invention are also provided. Preferred expression vectors are replicable DNA constructs in which a DNA sequence encoding nGPCR-x is operably linked or connected to suitable control sequences capable of effecting the expression of the nGPCR-x in a suitable host. DNA regions are operably linked or connected when they are functionally related to each other. For example, a promoter is operably linked or connected to a coding sequence if it controls the transcription of the sequence. Amplification vectors do not require expression control domains, but rather need only the ability to replicate in a host, usually conferred by an origin of replication, and a selection gene to facilitate recognition of transformants. The need for control sequences in the expression vector will vary depending upon the host selected and the transformation method chosen. Generally, control sequences include a transcriptional promoter, an optional operator sequence to control transcription, a sequence encoding suitable mRNA ribosomal binding and sequences which control the termination of transcription and translation.

Preferred vectors preferably contain a promoter that is recognized by the host organism. The promoter sequences of the present invention may be prokaryotic, eukaryotic or viral. Examples of suitable prokaryotic sequences include the P_R and P_L promoters of bacteriophage

lambda (The bacteriophage Lambda, Hershey, A. D., Ed., Cold Spring Harbor Press, Cold Spring Harbor, NY (1973), which is incorporated herein by reference in its entirety; Lambda II, Hendrix, R. W., Ed., Cold Spring Harbor Press, Cold Spring Harbor, NY (1980), which is incorporated herein by reference in its entirety); the trp, recA, heat shock, and lacZ promoters of *E. coli* and the SV40 early promoter (Benoist *et al. Nature*, 1981, 290, 304-310, which is incorporated herein by reference in its entirety). Additional promoters include, but are not limited to, mouse mammary tumor virus, long terminal repeat of human immunodeficiency virus, maloney virus, cytomegalovirus immediate early promoter, Epstein Barr virus, Rous sarcoma virus, human actin, human myosin, human hemoglobin, human muscle creatine, and human metallothionein.

Additional regulatory sequences can also be included in preferred vectors. Preferred examples of suitable regulatory sequences are represented by the Shine-Dalgarno of the replicase gene of the phage MS-2 and of the gene cII of bacteriophage lambda. The Shine-Dalgarno sequence may be directly followed by DNA encoding nGPCR-x and result in the expression of the mature nGPCR-x protein.

Moreover, suitable expression vectors can include an appropriate marker that allows the screening of the transformed host cells. The transformation of the selected host is carried out using any one of the various techniques well known to the expert in the art and described in Sambrook *et al., supra*.

An origin of replication can also be provided either by construction of the vector to include an exogenous origin or may be provided by the host cell chromosomal replication mechanism. If the vector is integrated into the host cell chromosome, the latter may be sufficient. Alternatively, rather than using vectors which contain viral origins of replication, one skilled in the art can transform mammalian cells by the method of co-transformation with a selectable marker and nGPCR-x DNA. An example of a suitable marker is dihydrofolate reductase (DHFR) or thymidine kinase (*see*, U.S. Patent No. 4,399,216).

Nucleotide sequences encoding GPCR-x may be recombined with vector DNA in accordance with conventional techniques, including blunt-ended or staggered-ended termini for ligation, restriction enzyme digestion to provide appropriate termini, filling in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and ligation with appropriate ligases. Techniques for such manipulation are disclosed by Sambrook *et al., supra* and are well known in the art. Methods for construction of mammalian expression vectors are disclosed in, for example, Okayama *et al., Mol. Cell. Biol.*, 1983, 3, 280, Cosman *et al., Mol.*

Immunol., 1986, 23, 935, Cosman *et al.*, *Nature*, 1984, 312, 768, EP-A-0367566, and WO 91/18982, each of which is incorporated herein by reference in its entirety.

Host cells

According to another aspect of the invention, host cells are provided, including
5 prokaryotic and eukaryotic cells, comprising a polynucleotide of the invention (or vector of the invention) in a manner that permits expression of the encoded nGPCR-x polypeptide. Polynucleotides of the invention may be introduced into the host cell as part of a circular plasmid, or as linear DNA comprising an isolated protein coding region or a viral vector. Methods for introducing DNA into the host cell that are well known and routinely practiced in
10 the art include transformation, transfection, electroporation, nuclear injection, or fusion with carriers such as liposomes, micelles, ghost cells, and protoplasts. Expression systems of the invention include bacterial, yeast, fungal, plant, insect, invertebrate, vertebrate, and mammalian cells systems.

The invention provides host cells that are transformed or transfected (stably or
15 transiently) with polynucleotides of the invention or vectors of the invention. As stated above, such host cells are useful for amplifying the polynucleotides and also for expressing the nGPCR-x polypeptide or fragment thereof encoded by the polynucleotide.

In still another related embodiment, the invention provides a method for producing a nGPCR-x polypeptide (or fragment thereof) comprising the steps of growing a host cell of the
20 invention in a nutrient medium and isolating the polypeptide or variant thereof from the cell or the medium. Because nGPCR-x is a seven transmembrane receptor, it will be appreciated that, for some applications, such as certain activity assays, the preferable isolation may involve isolation of cell membranes containing the polypeptide embedded therein, whereas for other applications a more complete isolation may be preferable.

25 According to some aspects of the present invention, transformed host cells having an expression vector comprising any of the nucleic acid molecules described above are provided. Expression of the nucleotide sequence occurs when the expression vector is introduced into an appropriate host cell. Suitable host cells for expression of the polypeptides of the invention include, but are not limited to, prokaryotes, yeast, and eukaryotes. If a prokaryotic expression
30 vector is employed, then the appropriate host cell would be any prokaryotic cell capable of expressing the cloned sequences. Suitable prokaryotic cells include, but are not limited to, bacteria of the genera *Escherichia*, *Bacillus*, *Salmonella*, *Pseudomonas*, *Streptomyces*, and *Staphylococcus*.

If an eukaryotic expression vector is employed, then the appropriate host cell would be any eukaryotic cell capable of expressing the cloned sequence. Preferably, eukaryotic cells are cells of higher eukaryotes. Suitable eukaryotic cells include, but are not limited to, non-human mammalian tissue culture cells and human tissue culture cells. Preferred host cells include, but are not limited to, insect cells, HeLa cells, Chinese hamster ovary cells (CHO cells), African green monkey kidney cells (COS cells), human 293 cells, and murine 3T3 fibroblasts.

Propagation of such cells in cell culture has become a routine procedure (*see*, Tissue Culture, Academic Press, Kruse and Patterson, eds. (1973), which is incorporated herein by reference in its entirety).

In addition, a yeast host may be employed as a host cell. Preferred yeast cells include, but are not limited to, the genera *Saccharomyces*, *Pichia*, and *Kluveromyces*. Preferred yeast hosts are *S. cerevisiae* and *P. pastoris*. Preferred yeast vectors can contain an origin of replication sequence from a 2T yeast plasmid, an autonomously replication sequence (ARS), a promoter region, sequences for polyadenylation, sequences for transcription termination, and a selectable marker gene. Shuttle vectors for replication in both yeast and *E. coli* are also included herein.

Alternatively, insect cells may be used as host cells. In a preferred embodiment, the polypeptides of the invention are expressed using a baculovirus expression system (*see*, Luckow *et al.*, *Bio/Technology*, 1988, 6, 47, Baculovirus Expression Vectors: A Laboratory Manual, O'Rielly *et al.* (Eds.), W.H. Freeman and Company, New York, 1992, and U.S. Patent No. 4,879,236, each of which is incorporated herein by reference in its entirety). In addition, the MAXBAC™ complete baculovirus expression system (Invitrogen) can, for example, be used for production in insect cells.

Host cells of the invention are a valuable source of immunogen for development of antibodies specifically immunoreactive with nGPCR-x. Host cells of the invention are also useful in methods for the large-scale production of nGPCR-x polypeptides wherein the cells are grown in a suitable culture medium and the desired polypeptide products are isolated from the cells, or from the medium in which the cells are grown, by purification methods known in the art, *e.g.*, conventional chromatographic methods including immunoaffinity chromatography, receptor affinity chromatography, hydrophobic interaction chromatography, lectin affinity chromatography, size exclusion filtration, cation or anion exchange chromatography, high pressure liquid chromatography (HPLC), reverse phase HPLC, and the like. Still other methods of purification include those methods wherein the desired protein is expressed and purified as a

fusion protein having a specific tag, label, or chelating moiety that is recognized by a specific binding partner or agent. The purified protein can be cleaved to yield the desired protein, or can be left as an intact fusion protein. Cleavage of the fusion component may produce a form of the desired protein having additional amino acid residues as a result of the cleavage process.

5 Knowledge of nGPCR-x DNA sequences allows for modification of cells to permit, or increase, expression of endogenous nGPCR-x. Cells can be modified (*e.g.*, by homologous recombination) to provide increased expression by replacing, in whole or in part, the naturally occurring nGPCR-x promoter with all or part of a heterologous promoter so that the cells express nGPCR-x at higher levels. The heterologous promoter is inserted in such a manner that
10 it is operatively linked to endogenous nGPCR-x encoding sequences. (See, for example, PCT International Publication No. WO 94/12650, PCT International Publication No. WO 92/20808, and PCT International Publication No. WO 91/09955.) It is also contemplated that, in addition to heterologous promoter DNA, amplifiable marker DNA (*e.g.*, *ada*, *dhfr*, and the multifunctional CAD gene which encodes carbamoyl phosphate synthase, aspartate
15 transcarbamylase, and dihydroorotase) and/or intron DNA may be inserted along with the heterologous promoter DNA. If linked to the nGPCR-x coding sequence, amplification of the marker DNA by standard selection methods results in co-amplification of the nGPCR-x coding sequences in the cells.

Knock-outs

20 The DNA sequence information provided by the present invention also makes possible the development (*e.g.*, by homologous recombination or "knock-out" strategies; see Capecchi, *Science* 244:1288-1292 (1989), which is incorporated herein by reference in its entirety) of animals that fail to express functional nGPCR-x or that express a variant of nGPCR-x. Such animals (especially small laboratory animals such as rats, rabbits, and mice) are useful as
25 models for studying the *in vivo* activities of nGPCR-x and modulators of nGPCR-x.

Antisense

Also made available by the invention are anti-sense polynucleotides that recognize and hybridize to polynucleotides encoding nGPCR-x. Full-length and fragment anti-sense polynucleotides are provided. Fragment antisense molecules of the invention include (i) those
30 that specifically recognize and hybridize to nGPCR-x RNA (as determined by sequence comparison of DNA encoding nGPCR-x to DNA encoding other known molecules). Identification of sequences unique to nGPCR-x encoding polynucleotides can be deduced through use of any publicly available sequence database, and/or through use of commercially

available sequence comparison programs. After identification of the desired sequences, isolation through restriction digestion or amplification using any of the various polymerase chain reaction techniques well known in the art can be performed. Anti-sense polynucleotides are particularly relevant to regulating expression of nGPCR-x by those cells expressing nGPCR-x mRNA.

5 Antisense nucleic acids (preferably 10 to 30 base-pair oligonucleotides) capable of specifically binding to nGPCR-x expression control sequences or nGPCR-x RNA are introduced into cells (e.g., by a viral vector or colloidal dispersion system such as a liposome). The antisense nucleic acid binds to the nGPCR-x target nucleotide sequence in the cell and prevents transcription and/or translation of the target sequence. Phosphorothioate and methylphosphonate
10 antisense oligonucleotides are specifically contemplated for therapeutic use by the invention. The antisense oligonucleotides may be further modified by adding poly-L-lysine, transferrin polylysine, or cholesterol moieties at their 5' end. Suppression of nGPCR-x expression at either the transcriptional or translational level is useful to generate cellular or animal models for diseases/conditions characterized by aberrant nGPCR-x expression.

15 Antisense oligonucleotides, or fragments of sequences selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:67, or sequences complementary or homologous thereto, derived from the nucleotide sequences of the present invention encoding nGPCR-x are useful as diagnostic tools for probing gene expression in various tissues. For example, tissue can be probed *in situ* with oligonucleotide probes carrying detectable groups by conventional
20 autoradiography techniques to investigate native expression of this enzyme or pathological conditions relating thereto. Antisense oligonucleotides are preferably directed to regulatory regions of sequences selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:67, or mRNA corresponding thereto, including, but not limited to, the initiation codon, TATA box, enhancer sequences, and the like.

25 **Transcription factors**

The nGPCR-x sequences taught in the present invention facilitate the design of novel transcription factors for modulating nGPCR-x expression in native cells and animals, and cells transformed or transfected with nGPCR-x polynucleotides. For example, the Cys₂-His₂ zinc finger proteins, which bind DNA via their zinc finger domains, have been shown to be amenable
30 to structural changes that lead to the recognition of different target sequences. These artificial zinc finger proteins recognize specific target sites with high affinity and low dissociation constants, and are able to act as gene switches to modulate gene expression. Knowledge of the particular nGPCR-x target sequence of the present invention facilitates the engineering of zinc

finger proteins specific for the target sequence using known methods such as a combination of structure-based modeling and screening of phage display libraries (Segal *et al.*, *Proc. Natl. Acad. Sci. USA* 96:2758-2763 (1999); Liu *et al.*, *Proc. Natl. Acad. Sci. USA* 94:5525-5530 (1997); Greisman *et al.*, *Science* 275:657-661 (1997); Choo *et al.*, *J. Mol. Biol.* 273:525-532 (1997)). Each zinc finger domain usually recognizes three or more base pairs. Since a recognition sequence of 18 base pairs is generally sufficient in length to render it unique in any known genome, a zinc finger protein consisting of 6 tandem repeats of zinc fingers would be expected to ensure specificity for a particular sequence (Segal *et al.*). The artificial zinc finger repeats, designed based on nGPCR-x sequences, are fused to activation or repression domains to promote or suppress nGPCR-x expression (Liu *et al.*). Alternatively, the zinc finger domains can be fused to the TATA box-binding factor (TBP) with varying lengths of linker region between the zinc finger peptide and the TBP to create either transcriptional activators or repressors (Kim *et al.*, *Proc. Natl. Acad. Sci. USA* 94:3616-3620 (1997). Such proteins and polynucleotides that encode them, have utility for modulating nGPCR-x expression *in vivo* in both native cells, animals and humans; and/or cells transfected with nGPCR-x-encoding sequences. The novel transcription factor can be delivered to the target cells by transfecting constructs that express the transcription factor (gene therapy), or by introducing the protein. Engineered zinc finger proteins can also be designed to bind RNA sequences for use in therapeutics as alternatives to antisense or catalytic RNA methods (McColl *et al.*, *Proc. Natl. Acad. Sci. USA* 96:9521-9526 (1997); Wu *et al.*, *Proc. Natl. Acad. Sci. USA* 92:344-348 (1995)). The present invention contemplates methods of designing such transcription factors based on the gene sequence of the invention, as well as customized zinc finger proteins, that are useful to modulate nGPCR-x expression in cells (native or transformed) whose genetic complement includes these sequences.

Polypeptides

The invention also provides purified and isolated mammalian nGPCR-x polypeptides encoded by a polynucleotide of the invention. Presently preferred is a human nGPCR-x polypeptide comprising the amino acid sequence set out in sequences selected from the group consisting of SEQ ID NO:68 to SEQ ID NO:136, or fragments thereof comprising an epitope specific to the polypeptide. By "epitope specific to" is meant a portion of the nGPCR receptor that is recognizable by an antibody that is specific for the nGPCR, as defined in detail below.

Although the sequences provided are particular human sequences, the invention is intended to include within its scope other human allelic variants; non-human mammalian forms of nGPCR-x, and other vertebrate forms of nGPCR-x.

It will be appreciated that extracellular epitopes are particularly useful for generating and screening for antibodies and other binding compounds that bind to receptors such as nGPCR-x. Thus, in another preferred embodiment, the invention provides a purified and isolated polypeptide comprising at least one extracellular domain (e.g., the N-terminal extracellular domain or one of the three extracellular loops) of nGPCR-x. Purified and isolated polypeptides comprising the N-terminal extracellular domain of nGPCR-x are highly preferred. Also preferred is a purified and isolated polypeptide comprising a nGPCR-x fragment selected from the group consisting of the N-terminal extracellular domain of nGPCR-x, transmembrane domains of nGPCR-x, an extracellular loop connecting transmembrane domains of nGPCR-x, an intracellular loop connecting transmembrane domains of nGPCR-x, the C-terminal cytoplasmic region of nGPCR-x, and fusions thereof. Such fragments may be continuous portions of the native receptor. However, it will also be appreciated that knowledge of the nGPCR-x gene and protein sequences as provided herein permits recombining of various domains that are not contiguous in the native protein. Using a FORTRAN computer program called "tmrest.all" (Parodi *et al.*, *Comput. Appl. Biosci.* 5:527-535 (1994)), nGPCR-x was shown to contain transmembrane-spanning domains.

The invention also embraces polypeptides that have at least 99%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55% or at least 50% identity and/or homology to the preferred polypeptide of the invention.

Percent amino acid sequence "identity" with respect to the preferred polypeptide of the invention is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with the residues in the nGPCR-x sequence after aligning both sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Percent sequence "homology" with respect to the preferred polypeptide of the invention is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with the residues in the nGPCR-x sequence after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and also considering any conservative substitutions as part of the sequence identity.

In one aspect, percent homology is calculated as the percentage of amino acid residues in the smaller of two sequences which align with identical amino acid residue in the sequence being compared, when four gaps in a length of 100 amino acids may be introduced to maximize alignment (Dayhoff, in *Atlas of Protein Sequence and Structure*, Vol. 5, p. 124, National

Biochemical Research Foundation, Washington, D.C. (1972), incorporated herein by reference in its entirety).

Polypeptides of the invention may be isolated from natural cell sources or may be chemically synthesized, but are preferably produced by recombinant procedures involving host
5 cells of the invention. Use of mammalian host cells is expected to provide for such post-translational modifications (e.g., glycosylation, truncation, lipidation, and phosphorylation) as may be needed to confer optimal biological activity on recombinant expression products of the invention. Glycosylated and non-glycosylated forms of nGPCR-x polypeptides are embraced by the invention.

10 The invention also embraces variant (or analog) nGPCR-x polypeptides. In one example, insertion variants are provided wherein one or more amino acid residues supplement a nGPCR-x amino acid sequence. Insertions may be located at either or both termini of the protein, or may be positioned within internal regions of the nGPCR-x amino acid sequence. Insertional variants with additional residues at either or both termini can include, for example, fusion proteins and
15 proteins including amino acid tags or labels.

Insertion variants include nGPCR-x polypeptides wherein one or more amino acid residues are added to a nGPCR-x acid sequence or to a biologically active fragment thereof.

Variant products of the invention also include mature nGPCR-x products, *i.e.*, nGPCR-x products wherein leader or signal sequences are removed, with additional amino terminal
20 residues. The additional amino terminal residues may be derived from another protein, or may include one or more residues that are not identifiable as being derived from specific proteins. nGPCR-x products with an additional methionine residue at position -1 (Met⁻¹-nGPCR-x) are contemplated, as are variants with additional methionine and lysine residues at positions -2 and -1 (Met⁻²-Lys⁻¹-nGPCR-x). Variants of nGPCR-x with additional Met, Met-Lys, Lys residues
25 (or one or more basic residues in general) are particularly useful for enhanced recombinant protein production in bacterial host cells.

The invention also embraces nGPCR-x variants having additional amino acid residues that result from use of specific expression systems. For example, use of commercially available vectors that express a desired polypeptide as part of a glutathione-S-transferase (GST) fusion
30 product provides the desired polypeptide having an additional glycine residue at position -1 after cleavage of the GST component from the desired polypeptide. Variants that result from expression in other vector systems are also contemplated.

Insertional variants also include fusion proteins wherein the amino terminus and/or the carboxy terminus of nGPCR-x is/are fused to another polypeptide.

In another aspect, the invention provides deletion variants wherein one or more amino acid residues in a nGPCR-x polypeptide are removed. Deletions can be effected at one or both termini of the nGPCR-x polypeptide, or with removal of one or more non-terminal amino acid residues of nGPCR-x. Deletion variants, therefore, include all fragments of a nGPCR-x polypeptide.

The invention also embraces polypeptide fragments of sequences selected from the group consisting of SEQ ID NO:68 to SEQ ID NO:136, wherein the fragments maintain biological (*e.g.*, ligand binding and/or intracellular signaling) immunological properties of a nGPCR-x polypeptide.

In one preferred embodiment of the invention, an isolated nucleic acid molecule comprises a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence homologous to sequences selected from the group consisting of SEQ ID NO:68 to SEQ ID NO:136, and fragments thereof, wherein the nucleic acid molecule encoding at least a portion of nGPCR-x. In a more preferred embodiment, the isolated nucleic acid molecule comprises a sequence that encodes a polypeptide comprising sequences selected from the group consisting of SEQ ID NO:68 to SEQ ID NO:136, and fragments thereof.

As used in the present invention, polypeptide fragments comprise at least 5, 10, 15, 20, 25, 30, 35, or 40 consecutive amino acids of sequences selected from the group consisting of SEQ ID NO:68 to SEQ ID NO:136. Preferred polypeptide fragments display antigenic properties unique to, or specific for, human nGPCR-x and its allelic and species homologs. Fragments of the invention having the desired biological and immunological properties can be prepared by any of the methods well known and routinely practiced in the art.

In still another aspect, the invention provides substitution variants of nGPCR-x polypeptides. Substitution variants include those polypeptides wherein one or more amino acid residues of a nGPCR-x polypeptide are removed and replaced with alternative residues. In one aspect, the substitutions are conservative in nature; however, the invention embraces substitutions that are also non-conservative. Conservative substitutions for this purpose may be defined as set out in Tables 2, 3, or 4 below.

Variant polypeptides include those wherein conservative substitutions have been introduced by modification of polynucleotides encoding polypeptides of the invention. Amino acids can be classified according to physical properties and contribution to secondary and

tertiary protein structure. A conservative substitution is recognized in the art as a substitution of one amino acid for another amino acid that has similar properties. Exemplary conservative substitutions are set out in Table 2 (from WO 97/09433, page 10, published March 13, 1997 (PCT/GB96/02197, filed 9/6/96), immediately below.

5

Table 2

Conservative Substitutions I

<u>SIDE CHAIN CHARACTERISTIC</u>	<u>AMINO ACID</u>
Aliphatic	
Non-polar	G A P I L V
Polar - uncharged	C S T M N Q
Polar - charged	D E K R
Aromatic	H F W Y
Other	N Q D E

Alternatively, conservative amino acids can be grouped as described in Lehninger, (*Biochemistry*, Second Edition; Worth Publishers, Inc. NY, NY (1975), pp.71-77) as set out in Table 3, below.

10

Table 3

Conservative Substitutions II

<u>SIDE CHAIN CHARACTERISTIC</u>	<u>AMINO ACID</u>
Non-polar (hydrophobic)	
A. Aliphatic:	A L I V P
B. Aromatic:	F W
C. Sulfur-containing:	M
D. Borderline:	G
Uncharged-polar	
A. Hydroxyl:	S T Y
B. Amides:	N Q
C. Sulfhydryl:	C
D. Borderline:	G
Positively Charged (Basic):	K R H
Negatively Charged (Acidic):	D E

As still another alternative, exemplary conservative substitutions are set out in Table 4,

15 below.

Table 4

Conservative Substitutions III

Original Residue	Exemplary Substitution
---------------------	------------------------

Ala (A)	Val, Leu, Ile
Arg (R)	Lys, Gln, Asn
Asn (N)	Gln, His, Lys, Arg
Asp (D)	Glu
Cys (C)	Ser
Gln (Q)	Asn
Glu (E)	Asp
His (H)	Asn, Gln, Lys, Arg
Ile (I)	Leu, Val, Met, Ala, Phe,
Leu (L)	Ile, Val, Met, Ala, Phe
Lys (K)	Arg, Gln, Asn
Met (M)	Leu, Phe, Ile
Phe (F)	Leu, Val, Ile, Ala
Pro (P)	Gly
Ser (S)	Thr
Thr (T)	Ser
Trp (W)	Tyr
Tyr (Y)	Trp, Phe, Thr, Ser
Val (V)	Ile, Leu, Met, Phe, Ala

It should be understood that the definition of polypeptides of the invention is intended to include polypeptides bearing modifications other than insertion, deletion, or substitution of amino acid residues. By way of example, the modifications may be covalent in nature, and include for example, chemical bonding with polymers, lipids, other organic, and inorganic moieties. Such derivatives may be prepared to increase circulating half-life of a polypeptide, or may be designed to improve the targeting capacity of the polypeptide for desired cells, tissues, or organs. Similarly, the invention further embraces nGPCR-x polypeptides that have been covalently modified to include one or more water-soluble polymer attachments such as polyethylene glycol, polyoxyethylene glycol, or polypropylene glycol. Variants that display ligand binding properties of native nGPCR-x and are expressed at higher levels, as well as variants that provide for constitutively active receptors, are particularly useful in assays of the invention; the variants are also useful in providing cellular, tissue and animal models of diseases/conditions characterized by aberrant nGPCR-x activity.

In a related embodiment, the present invention provides compositions comprising purified polypeptides of the invention. Preferred compositions comprise, in addition to the polypeptide of the invention, a pharmaceutically acceptable (*i.e.*, sterile and non-toxic) liquid, semisolid, or solid diluent that serves as a pharmaceutical vehicle, excipient, or medium. Any diluent known in the art may be used. Exemplary diluents include, but are not limited to, water,

saline solutions, polyoxyethylene sorbitan monolaurate, magnesium stearate, methyl- and propylhydroxybenzoate, talc, alginates, starches, lactose, sucrose, dextrose, sorbitol, mannitol, glycerol, calcium phosphate, mineral oil, and cocoa butter.

5 Variants that display ligand binding properties of native nGPCR-x and are expressed at higher levels, as well as variants that provide for constitutively active receptors, are particularly useful in assays of the invention; the variants are also useful in assays of the invention and in providing cellular, tissue and animal models of diseases/conditions characterized by aberrant nGPCR-x activity.

10 The G protein-coupled receptor functions through a specific heterotrimeric guanine-nucleotide-binding regulatory protein (G-protein) coupled to the intracellular portion of the G protein-coupled receptor molecule. Accordingly, the G protein-coupled receptor has a specific affinity to G protein. G proteins specifically bind to guanine nucleotides. Isolation of G proteins provides a means to isolate guanine nucleotides. G Proteins may be isolated using commercially available anti-G protein antibodies or isolated G protein-coupled receptors.
15 Similarly, G proteins may be detected in a sample isolated using commercially available detectable anti-G protein antibodies or isolated G protein-coupled receptors.

According to the present invention, the isolated n-GPCR-x proteins of the present invention are useful to isolate and purify G proteins from samples such as cell lysates. Example 14 below sets forth an example of isolation of G proteins using isolated n-GPCR-x proteins.
20 Such methodology may be used in place of the use of commercially available anti-G protein antibodies which are used to isolate G proteins. Moreover, G proteins may be detected using n-GPCR-x proteins in place of commercially available detectable anti-G protein antibodies. Since n-GPCR-x proteins specifically bind to G proteins, they can be employed in any specific use where G protein specific affinity is required such as those uses where commercially available
25 anti-G protein antibodies are employed.

Antibodies

Also comprehended by the present invention are antibodies (e.g., monoclonal and polyclonal antibodies, single chain antibodies, chimeric antibodies, bifunctional/bispecific antibodies, humanized antibodies, human antibodies, and complementary determining region
30 (CDR)-grafted antibodies, including compounds which include CDR sequences which specifically recognize a polypeptide of the invention) specific for nGPCR-x or fragments thereof. Preferred antibodies of the invention are human antibodies that are produced and identified according to methods described in WO93/11236, published June 20, 1993, which is

incorporated herein by reference in its entirety. Antibody fragments, including Fab, Fab', F(ab')₂, and F_v, are also provided by the invention. The term "specific for," when used to describe antibodies of the invention, indicates that the variable regions of the antibodies of the invention recognize and bind nGPCR-x polypeptides exclusively (*i.e.*, are able to distinguish nGPCR-x polypeptides from other known GPCR polypeptides by virtue of measurable differences in binding affinity, despite the possible existence of localized sequence identity, homology, or similarity between nGPCR-x and such polypeptides). It will be understood that specific antibodies may also interact with other proteins (for example, *S. aureus* protein A or other antibodies in ELISA techniques) through interactions with sequences outside the variable region of the antibodies, and, in particular, in the constant region of the molecule. Screening assays to determine binding specificity of an antibody of the invention are well known and routinely practiced in the art. For a comprehensive discussion of such assays, see Harlow *et al.* (Eds.), *Antibodies A Laboratory Manual*; Cold Spring Harbor Laboratory; Cold Spring Harbor, NY (1988), Chapter 6. Antibodies that recognize and bind fragments of the nGPCR-x polypeptides of the invention are also contemplated, provided that the antibodies are specific for nGPCR-x polypeptides. Antibodies of the invention can be produced using any method well known and routinely practiced in the art.

The invention provides an antibody that is specific for the nGPCR-x of the invention. Antibody specificity is described in greater detail below. However, it should be emphasized that antibodies that can be generated from polypeptides that have previously been described in the literature and that are capable of fortuitously cross-reacting with nGPCR-x (*e.g.*, due to the fortuitous existence of a similar epitope in both polypeptides) are considered "cross-reactive" antibodies. Such cross-reactive antibodies are not antibodies that are "specific" for nGPCR-x. The determination of whether an antibody is specific for nGPCR-x or is cross-reactive with another known receptor is made using any of several assays, such as Western blotting assays, that are well known in the art. For identifying cells that express nGPCR-x and also for modulating nGPCR-x-ligand binding activity, antibodies that specifically bind to an extracellular epitope of the nGPCR-x are preferred.

In one preferred variation, the invention provides monoclonal antibodies. Hybridomas that produce such antibodies also are intended as aspects of the invention. In yet another variation, the invention provides a humanized antibody. Humanized antibodies are useful for *in vivo* therapeutic indications.

In another variation, the invention provides a cell-free composition comprising polyclonal antibodies, wherein at least one of the antibodies is an antibody of the invention specific for nGPCR-x. Antisera isolated from an animal is an exemplary composition, as is a composition comprising an antibody fraction of an antisera that has been resuspended in water or in another diluent, excipient, or carrier.

In still another related embodiment, the invention provides an anti-idiotypic antibody specific for an antibody that is specific for nGPCR-x.

It is well known that antibodies contain relatively small antigen binding domains that can be isolated chemically or by recombinant techniques. Such domains are useful nGPCR-x binding molecules themselves, and also may be reintroduced into human antibodies, or fused to toxins or other polypeptides. Thus, in still another embodiment, the invention provides a polypeptide comprising a fragment of a nGPCR-x-specific antibody, wherein the fragment and the polypeptide bind to the nGPCR-x. By way of non-limiting example, the invention provides polypeptides that are single chain antibodies and CDR-grafted antibodies.

Non-human antibodies may be humanized by any of the methods known in the art. In one method, the non-human CDRs are inserted into a human antibody or consensus antibody framework sequence. Further changes can then be introduced into the antibody framework to modulate affinity or immunogenicity.

Antibodies of the invention are useful for, *e.g.*, therapeutic purposes (by modulating activity of nGPCR-x), diagnostic purposes to detect or quantitate nGPCR-x, and purification of nGPCR-x. Kits comprising an antibody of the invention for any of the purposes described herein are also comprehended. In general, a kit of the invention also includes a control antigen for which the antibody is immunospecific.

Compositions

Mutations in the nGPCR-x gene that result in loss of normal function of the nGPCR-x gene product underlie nGPCR-x-related human disease states. The invention comprehends gene therapy to restore nGPCR-x activity to treat those disease states. Delivery of a functional nGPCR-x gene to appropriate cells is effected *ex vivo*, *in situ*, or *in vivo* by use of vectors, and more particularly viral vectors (*e.g.*, adenovirus, adeno-associated virus, or a retrovirus), or *ex vivo* by use of physical DNA transfer methods (*e.g.*, liposomes or chemical treatments). See, for example, Anderson, *Nature*, supplement to vol. 392, no. 6679, pp.25-20 (1998). For additional reviews of gene therapy technology see Friedmann, *Science*, 244: 1275-1281 (1989); Verma, *Scientific American*: 68-84 (1990); and Miller, *Nature*, 357: 455-460 (1992). Alternatively, it is

contemplated that in other human disease states, preventing the expression of, or inhibiting the activity of, nGPCR-x will be useful in treating disease states. It is contemplated that antisense therapy or gene therapy could be applied to negatively regulate the expression of nGPCR-x.

Another aspect of the present invention is directed to compositions, including
5 pharmaceutical compositions, comprising any of the nucleic acid molecules or recombinant expression vectors described above and an acceptable carrier or diluent. Preferably, the carrier or diluent is pharmaceutically acceptable. Suitable carriers are described in the most recent edition of *Remington's Pharmaceutical Sciences*, A. Osol, a standard reference text in this field,
10 which is incorporated herein by reference in its entirety. Preferred examples of such carriers or diluents include, but are not limited to, water, saline, Ringer's solution, dextrose solution, and 5% human serum albumin. Liposomes and nonaqueous vehicles such as fixed oils may also be used. The formulations are sterilized by commonly used techniques.

Also within the scope of the invention are compositions comprising polypeptides, polynucleotides, or antibodies of the invention that have been formulated with, *e.g.*, a
15 pharmaceutically acceptable carrier.

The invention also provides methods of using antibodies of the invention. For example, the invention provides a method for modulating ligand binding of a nGPCR-x comprising the step of contacting the nGPCR-x with an antibody specific for the nGPCR-x, under conditions wherein the antibody binds the receptor.

20 GPCRs that may be expressed in the brain provide an indication that aberrant nGPCR-x signaling activity may correlate with one or more neurological or psychological disorders. The invention also provides a method for treating a neurological or psychiatric disorder comprising the step of administering to a mammal in need of such treatment an amount of an antibody-like polypeptide of the invention that is sufficient to modulate ligand binding to a nGPCR-x in
25 neurons of the mammal. nGPCR-x may also be expressed in other tissues, including but not limited to, peripheral blood lymphocytes, pancreas, ovary, uterus, testis, salivary gland, thyroid gland, kidney, adrenal gland, liver, bone marrow, prostate, fetal liver, colon, muscle, and fetal brain, and may be found in many other tissues. Within the brain, nGPCR-x mRNA transcripts may be found in many tissues, including, but not limited to, frontal lobe, hypothalamus, pons,
30 cerebellum, caudate nucleus, and medulla. Tissues and brain regions where specific nGPCRs of the present invention are expressed are identified in the Examples below.

Kits

The present invention is also directed to kits, including pharmaceutical kits. The kits can comprise any of the nucleic acid molecules described above, any of the polypeptides described above, or any antibody which binds to a polypeptide of the invention as described above, as well as a negative control. The kit preferably comprises additional components, such as, for example, instructions, solid support, reagents helpful for quantification, and the like.

In another aspect, the invention features methods for detection of a polypeptide in a sample as a diagnostic tool for diseases or disorders, wherein the method comprises the steps of: (a) contacting the sample with a nucleic acid probe which hybridizes under hybridization assay conditions to a nucleic acid target region of a polypeptide having sequences selected from the group consisting of SEQ ID NO:68 to SEQ ID NO:136, said probe comprising the nucleic acid sequence encoding the polypeptide, fragments thereof, and the complements of the sequences and fragments; and (b) detecting the presence or amount of the probe:target region hybrid as an indication of the disease.

In preferred embodiments of the invention, the disease is selected from the group consisting of thyroid disorders (*e.g.* thyreotoxicosis, myxoedema); renal failure; inflammatory conditions (*e.g.*, Crohn's disease); diseases related to cell differentiation and homeostasis; rheumatoid arthritis; autoimmune disorders; movement disorders; CNS disorders (*e.g.*, pain including migraine; stroke; psychotic and neurological disorders, including anxiety, mental disorder, manic depression, anxiety, generalized anxiety disorder, post-traumatic-stress disorder, depression, bipolar disorder, delirium, dementia, severe mental retardation; dyskinesias, such as Huntington's disease or Tourette's Syndrome; attention disorders including attention deficit disorder (ADD) and attention deficit-hyperactivity disorder (ADHD), and degenerative disorders such as Parkinson's, Alzheimer's; movement disorders, including ataxias, supranuclear palsy, *etc.*); infections, such as viral infections caused by HIV-1 or HIV-2; metabolic and cardiovascular diseases and disorders (*e.g.*, type 2 diabetes, impaired glucose tolerance, dyslipidemia, obesity, anorexia, hypotension, hypertension, thrombosis, myocardial infarction, cardiomyopathies, atherosclerosis, *etc.*); proliferative diseases and cancers (*e.g.*, different cancers such as breast, colon, lung, *etc.*, and hyperproliferative disorders such as psoriasis, prostate hyperplasia, *etc.*); hormonal disorders (*e.g.*, male/female hormonal replacement, polycystic ovarian syndrome, alopecia, *etc.*); and sexual dysfunction, among others.

Kits may be designed to detect either expression of polynucleotides encoding these proteins or the proteins themselves in order to identify tissue as being neurological. For

example, oligonucleotide hybridization kits can be provided which include a container having an oligonucleotide probe specific for the n-GPCR-x-specific DNA and optionally, containers with positive and negative controls and/or instructions. Similarly, PCR kits can be provided which include a container having primers specific for the n-GPCR-x-specific sequences, DNA and optionally, containers with size markers, positive and negative controls and/or instructions.

Hybridization conditions should be such that hybridization occurs only with the genes in the presence of other nucleic acid molecules. Under stringent hybridization conditions only highly complementary nucleic acid sequences hybridize. Preferably, such conditions prevent hybridization of nucleic acids having 1 or 2 mismatches out of 20 contiguous nucleotides. Such conditions are defined supra.

The diseases for which detection of genes in a sample could be diagnostic include diseases in which nucleic acid (DNA and/or RNA) is amplified in comparison to normal cells. By "amplification" is meant increased numbers of DNA or RNA in a cell compared with normal cells.

The diseases that could be diagnosed by detection of nucleic acid in a sample preferably include central nervous system and metabolic diseases. The test samples suitable for nucleic acid probing methods of the present invention include, for example, cells or nucleic acid extracts of cells, or biological fluids. The samples used in the above-described methods will vary based on the assay format, the detection method and the nature of the tissues, cells or extracts to be assayed. Methods for preparing nucleic acid extracts of cells are well known in the art and can be readily adapted in order to obtain a sample that is compatible with the method utilized.

Alternatively, immunoassay kits can be provided which have containers container having antibodies specific for the n-GPCR-x-protein and optionally, containers with positive and negative controls and/or instructions.

Kits may also be provided useful in the identification of GPCR binding partners such as natural ligands or modulators (agonists or antagonists). Substances useful for treatment of disorders or diseases preferably show positive results in one or more *in vitro* assays for an activity corresponding to treatment of the disease or disorder in question. Substances that modulate the activity of the polypeptides preferably include, but are not limited to, antisense oligonucleotides, agonists and antagonists, and inhibitors of protein kinases.

Methods of inducing immune response

Another aspect of the present invention is directed to methods of inducing an immune response in a mammal against a polypeptide of the invention by administering to the mammal an

amount of the polypeptide sufficient to induce an immune response. The amount will be dependent on the animal species, size of the animal, and the like but can be determined by those skilled in the art.

Methods of identifying ligands

5 The invention also provides assays to identify compounds that bind nGPCR-x. One such assay comprises the steps of: (a) contacting a composition comprising a nGPCR-x with a compound suspected of binding nGPCR-x; and (b) measuring binding between the compound and nGPCR-x. In one variation, the composition comprises a cell expressing nGPCR-x on its surface. In another variation, isolated nGPCR-x or cell membranes comprising nGPCR-x are
10 employed. The binding may be measured directly, *e.g.*, by using a labeled compound, or may be measured indirectly by several techniques, including measuring intracellular signaling of nGPCR-x induced by the compound (or measuring changes in the level of nGPCR-x signaling). Following steps (a) and (b), compounds identified as binding nGPCR-x can be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate
15 binding to nGPCR-x.

 Specific binding molecules, including natural ligands and synthetic compounds, can be identified or developed using isolated or recombinant nGPCR-x products, nGPCR-x variants, or preferably, cells expressing such products. Binding partners are useful for purifying nGPCR-x products and detection or quantification of nGPCR-x products in fluid and tissue samples using
20 known immunological procedures. Binding molecules are also manifestly useful in modulating (*i.e.*, blocking, inhibiting or stimulating) biological activities of nGPCR-x, especially those activities involved in signal transduction.

 The DNA and amino acid sequence information provided by the present invention also makes possible identification of binding partner compounds with which a nGPCR-x polypeptide or polynucleotide will interact. Methods to identify binding partner compounds include solution
25 assays, *in vitro* assays wherein nGPCR-x polypeptides are immobilized, and cell-based assays. Identification of binding partner compounds of nGPCR-x polypeptides provides candidates for therapeutic or prophylactic intervention in pathologies associated with nGPCR-x normal and aberrant biological activity.

30 The invention includes several assay systems for identifying nGPCR-x binding partners. In solution assays, methods of the invention comprise the steps of (a) contacting a nGPCR-x polypeptide with one or more candidate binding partner compounds and (b) identifying the compounds that bind to the nGPCR-x polypeptide. Identification of the compounds that bind

the nGPCR-x polypeptide can be achieved by isolating the nGPCR-x polypeptide/binding partner complex, and separating the binding partner compound from the nGPCR-x polypeptide. An additional step of characterizing the physical, biological, and/or biochemical properties of the binding partner compound is also comprehended in another embodiment of the invention, wherein compounds identified as binding nGPCR-x can be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate binding to nGPCR-x. In one aspect, the nGPCR-x polypeptide/binding partner complex is isolated using an antibody immunospecific for either the nGPCR-x polypeptide or the candidate binding partner compound.

In still other embodiments, either the nGPCR-x polypeptide or the candidate binding partner compound comprises a label or tag that facilitates its isolation, and methods of the invention to identify binding partner compounds include a step of isolating the nGPCR-x polypeptide/binding partner complex through interaction with the label or tag. An exemplary tag of this type is a poly-histidine sequence, generally around six histidine residues, that permits isolation of a compound so labeled using nickel chelation. Other labels and tags, such as the FLAG® tag (Eastman Kodak, Rochester, NY), well known and routinely used in the art, are embraced by the invention.

In one variation of an *in vitro* assay, the invention provides a method comprising the steps of (a) contacting an immobilized nGPCR-x polypeptide with a candidate binding partner compound and (b) detecting binding of the candidate compound to the nGPCR-x polypeptide. In an alternative embodiment, the candidate binding partner compound is immobilized and binding of nGPCR-x is detected. Immobilization is accomplished using any of the methods well known in the art, including covalent bonding to a support, a bead, or a chromatographic resin, as well as non-covalent, high affinity interactions such as antibody binding, or use of streptavidin/biotin binding wherein the immobilized compound includes a biotin moiety. Detection of binding can be accomplished (i) using a radioactive label on the compound that is not immobilized, (ii) using of a fluorescent label on the non-immobilized compound, (iii) using an antibody immunospecific for the non-immobilized compound, (iv) using a label on the non-immobilized compound that excites a fluorescent support to which the immobilized compound is attached, as well as other techniques well known and routinely practiced in the art.

The invention also provides cell-based assays to identify binding partner compounds of a nGPCR-x polypeptide. In one embodiment, the invention provides a method comprising the steps of contacting a nGPCR-x polypeptide expressed on the surface of a cell with a candidate

binding partner compound and detecting binding of the candidate binding partner compound to the nGPCR-x polypeptide. In a preferred embodiment, the detection comprises detecting a calcium flux or other physiological event in the cell caused by the binding of the molecule.

Another aspect of the present invention is directed to methods of identifying compounds
5 that bind to either nGPCR-x or nucleic acid molecules encoding nGPCR-x, comprising contacting nGPCR-x, or a nucleic acid molecule encoding the same, with a compound, and determining whether the compound binds nGPCR-x or a nucleic acid molecule encoding the same. Binding can be determined by binding assays which are well known to the skilled artisan, including, but not limited to, gel-shift assays, Western blots, radiolabeled competition assay,
10 phage-based expression cloning, co-fractionation by chromatography, co-precipitation, cross linking, interaction trap/two-hybrid analysis, southwestern analysis, ELISA, and the like, which are described in, for example, *Current Protocols in Molecular Biology*, 1999, John Wiley & Sons, NY, which is incorporated herein by reference in its entirety. The compounds to be screened include (which may include compounds which are suspected to bind nGPCR-x, or a
15 nucleic acid molecule encoding the same), but are not limited to, extracellular, intracellular, biologic or chemical origin. The methods of the invention also embrace ligands, especially neuropeptides, that are attached to a label, such as a radiolabel (e.g., ^{125}I , ^{35}S , ^{32}P , ^{33}P , ^3H), a fluorescence label, a chemiluminescent label, an enzymic label and an immunogenic label. Modulators falling within the scope of the invention include, but are not limited to, non-peptide
20 molecules such as non-peptide mimetics, non-peptide allosteric effectors, and peptides. The nGPCR-x polypeptide or polynucleotide employed in such a test may either be free in solution, attached to a solid support, borne on a cell surface or located intracellularly or associated with a portion of a cell. One skilled in the art can, for example, measure the formation of complexes between nGPCR-x and the compound being tested. Alternatively, one skilled in the art can
25 examine the diminution in complex formation between nGPCR-x and its substrate caused by the compound being tested.

In another embodiment of the invention, high throughput screening for compounds having suitable binding affinity to nGPCR-x is employed. Briefly, large numbers of different test compounds are synthesized on a solid substrate. The peptide test compounds are contacted
30 with nGPCR-x and washed. Bound nGPCR-x is then detected by methods well known in the art. Purified polypeptides of the invention can also be coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies can be used to capture the protein and immobilize it on the solid support.

Generally, an expressed nGPCR-x can be used for HTS binding assays in conjunction with its defined ligand, in this case the corresponding neuropeptide that activates it. The identified peptide is labeled with a suitable radioisotope, including, but not limited to, ^{125}I , ^3H , ^{35}S or ^{32}P , by methods that are well known to those skilled in the art. Alternatively, the peptides
5 may be labeled by well-known methods with a suitable fluorescent derivative (Baindur *et al.*, *Drug Dev. Res.*, 1994, 33, 373-398; Rogers, *Drug Discovery Today*, 1997, 2, 156-160).

Radioactive ligand specifically bound to the receptor in membrane preparations made from the cell line expressing the recombinant protein can be detected in HTS assays in one of several standard ways, including filtration of the receptor-ligand complex to separate bound ligand from
10 unbound ligand (Williams, *Med. Res. Rev.*, 1991, 11, 147-184; Sweetnam *et al.*, *J. Natural Products*, 1993, 56, 441-455). Alternative methods include a scintillation proximity assay (SPA) or a FlashPlate format in which such separation is unnecessary (Nakayama, *Cur. Opinion Drug Disc. Dev.*, 1998, 1, 85-91 Bossé *et al.*, *J. Biomolecular Screening*, 1998, 3, 285-292.). Binding of fluorescent ligands can be detected in various ways, including fluorescence energy transfer
15 (FRET), direct spectrophotofluorometric analysis of bound ligand, or fluorescence polarization (Rogers, *Drug Discovery Today*, 1997, 2, 156-160; Hill, *Cur. Opinion Drug Disc. Dev.*, 1998, 1, 92-97).

Other assays may be used to identify specific ligands of a nGPCR-x receptor, including assays that identify ligands of the target protein through measuring direct binding of test ligands
20 to the target protein, as well as assays that identify ligands of target proteins through affinity ultrafiltration with ion spray mass spectroscopy/HPLC methods or other physical and analytical methods. Alternatively, such binding interactions are evaluated indirectly using the yeast two-hybrid system described in Fields *et al.*, *Nature*, 340:245-246 (1989), and Fields *et al.*, *Trends in Genetics*, 10:286-292 (1994), both of which are incorporated herein by reference in its entirety.
25 The two-hybrid system is a genetic assay for detecting interactions between two proteins or polypeptides. It can be used to identify proteins that bind to a known protein of interest, or to delineate domains or residues critical for an interaction. Variations on this methodology have been developed to clone genes that encode DNA binding proteins, to identify peptides that bind to a protein, and to screen for drugs. The two-hybrid system exploits the ability of a pair of
30 interacting proteins to bring a transcription activation domain into close proximity with a DNA binding domain that binds to an upstream activation sequence (UAS) of a reporter gene, and is generally performed in yeast. The assay requires the construction of two hybrid genes encoding (1) a DNA-binding domain that is fused to a first protein and (2) an activation domain fused to a

second protein. The DNA-binding domain targets the first hybrid protein to the UAS of the reporter gene; however, because most proteins lack an activation domain, this DNA-binding hybrid protein does not activate transcription of the reporter gene. The second hybrid protein, which contains the activation domain, cannot by itself activate expression of the reporter gene because it does not bind the UAS. However, when both hybrid proteins are present, the noncovalent interaction of the first and second proteins tethers the activation domain to the UAS, activating transcription of the reporter gene. For example, when the first protein is a GPCR gene product, or fragment thereof, that is known to interact with another protein or nucleic acid, this assay can be used to detect agents that interfere with the binding interaction. Expression of the reporter gene is monitored as different test agents are added to the system. The presence of an inhibitory agent results in lack of a reporter signal.

The yeast two-hybrid assay can also be used to identify proteins that bind to the gene product. In an assay to identify proteins that bind to a nGPCR-x receptor, or fragment thereof, a fusion polynucleotide encoding both a nGPCR-x receptor (or fragment) and a UAS binding domain (*i.e.*, a first protein) may be used. In addition, a large number of hybrid genes each encoding a different second protein fused to an activation domain are produced and screened in the assay. Typically, the second protein is encoded by one or more members of a total cDNA or genomic DNA fusion library, with each second protein-coding region being fused to the activation domain. This system is applicable to a wide variety of proteins, and it is not even necessary to know the identity or function of the second binding protein. The system is highly sensitive and can detect interactions not revealed by other methods; even transient interactions may trigger transcription to produce a stable mRNA that can be repeatedly translated to yield the reporter protein.

Other assays may be used to search for agents that bind to the target protein. One such screening method to identify direct binding of test ligands to a target protein is described in U.S. Patent No. 5,585,277, incorporated herein by reference in its entirety. This method relies on the principle that proteins generally exist as a mixture of folded and unfolded states, and continually alternate between the two states. When a test ligand binds to the folded form of a target protein (*i.e.*, when the test ligand is a ligand of the target protein), the target protein molecule bound by the ligand remains in its folded state. Thus, the folded target protein is present to a greater extent in the presence of a test ligand which binds the target protein, than in the absence of a ligand. Binding of the ligand to the target protein can be determined by any method that distinguishes between the folded and unfolded states of the target protein. The function of the target protein

need not be known in order for this assay to be performed. Virtually any agent can be assessed by this method as a test ligand, including, but not limited to, metals, polypeptides, proteins, lipids, polysaccharides, polynucleotides and small organic molecules.

Another method for identifying ligands of a target protein is described in Wieboldt *et al.*,
5 *Anal. Chem.*, 69:1683-1691 (1997), incorporated herein by reference in its entirety. This
technique screens combinatorial libraries of 20-30 agents at a time in solution phase for binding
to the target protein. Agents that bind to the target protein are separated from other library
components by simple membrane washing. The specifically selected molecules that are retained
on the filter are subsequently liberated from the target protein and analyzed by HPLC and
10 pneumatically assisted electrospray (ion spray) ionization mass spectroscopy. This procedure
selects library components with the greatest affinity for the target protein, and is particularly
useful for small molecule libraries.

Determining whether a test compound binds to nGPCR-x can also be accomplished by
measuring the intrinsic fluorescence of nGPCR-x and determining whether the intrinsic
15 fluorescence is modulated in the presence of the test compound. Preferably, the intrinsic
fluorescence of nGPCR-x is measured as a function of the tryptophan residue(s) of nGPCR-x.
Preferably, fluorescence of nGPCR-x is measured and compared to the fluorescence intensity of
nGPCR-x in the presence of the test compound, wherein a decrease in fluorescence intensity
indicates binding of the test compound to nGPCR-x. Preferred methodology is set forth in
20 "Principles of Fluorescence Spectroscopy" by Joseph R. Lakowicz, New York, Plenum Press,
1983 (ISBN 0306412853) and "Spectrophotometry And Spectrofluorometry" by C.L. Bashford
and D.A. Harris Oxford, Washington DC, IRL Press, 1987 (ISBN 0947946691), each of which
is incorporated herein by reference in its entirety.

Other embodiments of the invention comprise using competitive screening assays in
25 which neutralizing antibodies capable of binding a polypeptide of the invention specifically
compete with a test compound for binding to the polypeptide. In this manner, the antibodies can
be used to detect the presence of any peptide that shares one or more antigenic determinants
with nGPCR-x. Radiolabeled competitive binding studies are described in A.H. Lin *et al.*
Antimicrobial Agents and Chemotherapy, 1997, vol. 41, no. 10. pp. 2127-2131, the disclosure of
30 which is incorporated herein by reference in its entirety.

Identification of modulating agents

The invention also provides methods for identifying a modulator of binding between a
nGPCR-x and a nGPCR-x binding partner, comprising the steps of: (a) contacting a nGPCR-x

binding partner and a composition comprising a nGPCR-x in the presence and in the absence of a putative modulator compound; (b) detecting binding between the binding partner and the nGPCR-x; and (c) identifying a putative modulator compound or a modulator compound in view of decreased or increased binding between the binding partner and the nGPCR-x in the presence of the putative modulator, as compared to binding in the absence of the putative modulator. Following steps (a) and (b), compounds identified as modulating binding between nGPCR-x and an nGPCR-x binding partner can be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate modulation of binding to nGPCR-x.

nGPCR-x binding partners that stimulate nGPCR-x activity are useful as agonists in disease states or conditions characterized by insufficient nGPCR-x signaling (*e.g.*, as a result of insufficient activity of a nGPCR-x ligand). nGPCR-x binding partners that block ligand-mediated nGPCR-x signaling are useful as nGPCR-x antagonists to treat disease states or conditions characterized by excessive nGPCR-x signaling. In addition nGPCR-x modulators in general, as well as nGPCR-x polynucleotides and polypeptides, are useful in diagnostic assays for such diseases or conditions.

In another aspect, the invention provides methods for treating a disease or abnormal condition by administering to a patient in need of such treatment a substance that modulates the activity or expression of a polypeptide having sequences selected from the group consisting of SEQ ID NO:68 to SEQ ID NO:136.

Agents that modulate (*i.e.*, increase, decrease, or block) nGPCR-x activity or expression may be identified by incubating a putative modulator with a cell containing a nGPCR-x polypeptide or polynucleotide and determining the effect of the putative modulator on nGPCR-x activity or expression. The selectivity of a compound that modulates the activity of nGPCR-x can be evaluated by comparing its effects on nGPCR-x to its effect on other GPCR compounds. Following identification of compounds that modulate nGPCR-x activity or expression, such compounds can be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate their activity. Selective modulators may include, for example, antibodies and other proteins, peptides, or organic molecules that specifically bind to a nGPCR-x polypeptide or a nGPCR-x-encoding nucleic acid. Modulators of nGPCR-x activity will be therapeutically useful in treatment of diseases and physiological conditions in which normal or aberrant nGPCR-x activity is involved. nGPCR-x polynucleotides, polypeptides, and modulators may be used in the treatment of such diseases and conditions as infections, such as viral infections caused by HIV-1 or HIV-2; pain; cancers; metabolic and cardiovascular diseases and

disorders (*e.g.*, type 2 diabetes, impaired glucose tolerance, dyslipidemia, obesity, anorexia, hypotension, hypertension, thrombosis, myocardial infarction, cardiomyopathies, atherosclerosis, *etc.*); Parkinson's disease; and psychotic and neurological disorders, including anxiety, mental disorder, manic depression, schizophrenia, migraine, major depression, attention disorders including ADD and ADHD, delirium, dementia, severe mental retardation and dyskinesias, such as Huntington's disease or Tourette's Syndrome, among others. nGPCR-x polynucleotides and polypeptides, as well as nGPCR-x modulators, may also be used in diagnostic assays for such diseases or conditions.

Methods of the invention to identify modulators include variations on any of the methods described above to identify binding partner compounds, the variations including techniques wherein a binding partner compound has been identified and the binding assay is carried out in the presence and absence of a candidate modulator. A modulator is identified in those instances where binding between the nGPCR-x polypeptide and the binding partner compound changes in the presence of the candidate modulator compared to binding in the absence of the candidate modulator compound. A modulator that increases binding between the nGPCR-x polypeptide and the binding partner compound is described as an enhancer or activator, and a modulator that decreases binding between the nGPCR-x polypeptide and the binding partner compound is described as an inhibitor. Following identification of modulators, such compounds can be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate their activity as modulators.

The invention also comprehends high-throughput screening (HTS) assays to identify compounds that interact with or inhibit biological activity (*i.e.*, affect enzymatic activity, binding activity, *etc.*) of a nGPCR-x polypeptide. HTS assays permit screening of large numbers of compounds in an efficient manner. Cell-based HTS systems are contemplated to investigate nGPCR-x receptor-ligand interaction. HTS assays are designed to identify "hits" or "lead compounds" having the desired property, from which modifications can be designed to improve the desired property. Chemical modification of the "hit" or "lead compound" is often based on an identifiable structure/activity relationship between the "hit" and the nGPCR-x polypeptide.

Another aspect of the present invention is directed to methods of identifying compounds which modulate (*i.e.*, increase or decrease) activity of nGPCR-x comprising contacting nGPCR-x with a compound, and determining whether the compound modifies activity of nGPCR-x. The activity in the presence of the test compared is measured to the activity in the absence of the test compound. Where the activity of the sample containing the test compound is higher than the

activity in the sample lacking the test compound, the compound will have increased activity. Similarly, where the activity of the sample containing the test compound is lower than the activity in the sample lacking the test compound, the compound will have inhibited activity. Following identification of compounds that modulate an activity of nGPCR-x, such compounds
5 can be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate their activity.

The present invention is particularly useful for screening compounds by using nGPCR-x in any of a variety of drug screening techniques. The compounds to be screened include (which may include compounds which are suspected to modulate nGPCR-x activity), but are not limited
10 to, extracellular, intracellular, biologic or chemical origin. The nGPCR-x polypeptide employed in such a test may be in any form, preferably, free in solution, attached to a solid support, borne on a cell surface or located intracellularly. One skilled in the art can, for example, measure the formation of complexes between nGPCR-x and the compound being tested. Alternatively, one skilled in the art can examine the diminution in complex formation between nGPCR-x and its
15 substrate caused by the compound being tested.

The activity of nGPCR-x polypeptides of the invention can be determined by, for example, examining the ability to bind or be activated by chemically synthesized peptide ligands. Alternatively, the activity of nGPCR-x polypeptides can be assayed by examining their ability to bind calcium ions, hormones, chemokines, neuropeptides, neurotransmitters,
20 nucleotides, lipids, odorants, and photons. Alternatively, the activity of the nGPCR-x polypeptides can be determined by examining the activity of effector molecules including, but not limited to, adenylate cyclase, phospholipases and ion channels. Thus, modulators of nGPCR-x polypeptide activity may alter a GPCR receptor function, such as a binding property of a receptor or an activity such as G protein-mediated signal transduction or membrane
25 localization. In various embodiments of the method, the assay may take the form of an ion flux assay, a yeast growth assay, a non-hydrolyzable GTP assay such as a [³⁵S]-GTP γS assay, a cAMP assay, an inositol triphosphate assay, a diacylglycerol assay, an Aequorin assay, a Luciferase assay, a FLIPR assay for intracellular Ca²⁺ concentration, a mitogenesis assay, a MAP Kinase activity assay, an arachidonic acid release assay (*e.g.*, using [³H]-arachidonic acid),
30 and an assay for extracellular acidification rates, as well as other binding or function-based assays of nGPCR-x activity that are generally known in the art. In several of these embodiments, the invention comprehends the inclusion of any of the G proteins known in the art, such as G₁₆, G₁₅, or chimeric G_{qds}, G_{qs5}, G_{qo5}, G_{q25}, and the like. nGPCR-x activity can be

determined by methodologies that are used to assay for FaRP activity, which is well known to those skilled in the art. Biological activities of nGPCR-x receptors according to the invention include, but are not limited to, the binding of a natural or an unnatural ligand, as well as any one of the functional activities of GPCRs known in the art. Non-limiting examples of GPCR activities include transmembrane signaling of various forms, which may involve G protein association and/or the exertion of an influence over G protein binding of various guanidylate nucleotides; another exemplary activity of GPCRs is the binding of accessory proteins or polypeptides that differ from known G proteins.

The modulators of the invention exhibit a variety of chemical structures, which can be generally grouped into non-peptide mimetics of natural GPCR receptor ligands, peptide and non-peptide allosteric effectors of GPCR receptors, and peptides that may function as activators or inhibitors (competitive, uncompetitive and non-competitive) (e.g., antibody products) of GPCR receptors. The invention does not restrict the sources for suitable modulators, which may be obtained from natural sources such as plant, animal or mineral extracts, or non-natural sources such as small molecule libraries, including the products of combinatorial chemical approaches to library construction, and peptide libraries. Examples of peptide modulators of GPCR receptors exhibit the following primary structures: GLGPRPLRFamide, GNSFLRFamide, GGPQGPLRFamide, GPSGPLRFamide, PDVDHVFLRFamide, and pyro-EDVDHVFLRFamide.

Other assays can be used to examine enzymatic activity including, but not limited to, photometric, radiometric, HPLC, electrochemical, and the like, which are described in, for example, *Enzyme Assays: A Practical Approach*, eds. R. Eisinger and M. J. Danson, 1992, Oxford University Press, which is incorporated herein by reference in its entirety.

The use of cDNAs encoding GPCRs in drug discovery programs is well-known; assays capable of testing thousands of unknown compounds per day in high-throughput screens (HTSs) are thoroughly documented. The literature is replete with examples of the use of radiolabelled ligands in HTS binding assays for drug discovery (see Williams, *Medicinal Research Reviews*, 1991, 11, 147-184.; Sweetnam, *et al.*, *J. Natural Products*, 1993, 56, 441-455 for review). Recombinant receptors are preferred for binding assay HTS because they allow for better specificity (higher relative purity), provide the ability to generate large amounts of receptor material, and can be used in a broad variety of formats (see Hodgson, *Bio/Technology*, 1992, 10, 973-980; each of which is incorporated herein by reference in its entirety).

A variety of heterologous systems is available for functional expression of recombinant receptors that are well known to those skilled in the art. Such systems include bacteria (Strosberg, *et al.*, *Trends in Pharmacological Sciences*, 1992, 13, 95-98), yeast (Pausch, *Trends in Biotechnology*, 1997, 15, 487-494), several kinds of insect cells (Vanden Broeck, *Int. Rev. Cytology*, 1996, 164, 189-268), amphibian cells (Jayawickreme *et al.*, *Current Opinion in Biotechnology*, 1997, 8, 629-634) and several mammalian cell lines (CHO, HEK293, COS, etc.; see Gerhardt, *et al.*, *Eur. J. Pharmacology*, 1997, 334, 1-23). These examples do not preclude the use of other possible cell expression systems, including cell lines obtained from nematodes (PCT application WO 98/37177).

In preferred embodiments of the invention, methods of screening for compounds that modulate nGPCR-x activity comprise contacting test compounds with nGPCR-x and assaying for the presence of a complex between the compound and nGPCR-x. In such assays, the ligand is typically labeled. After suitable incubation, free ligand is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of the particular compound to bind to nGPCR-x.

It is well known that activation of heterologous receptors expressed in recombinant systems results in a variety of biological responses, which are mediated by G proteins expressed in the host cells. Occupation of a GPCR by an agonist results in exchange of bound GDP for GTP at a binding site on the G_{α} subunit; one can use a radioactive, non-hydrolyzable derivative of GTP, $GTP\gamma[^{35}S]$, to measure binding of an agonist to the receptor (Sim *et al.*, *Neuroreport*, 1996, 7, 729-733). One can also use this binding to measure the ability of antagonists to bind to the receptor by decreasing binding of $GTP\gamma[^{35}S]$ in the presence of a known agonist. One could therefore construct a HTS based on $GTP\gamma[^{35}S]$ binding, though this is not the preferred method.

The G proteins required for functional expression of heterologous GPCRs can be native constituents of the host cell or can be introduced through well-known recombinant technology. The G proteins can be intact or chimeric. Often, a nearly universally competent G protein (e.g., $G_{\alpha 16}$) is used to couple any given receptor to a detectable response pathway. G protein activation results in the stimulation or inhibition of other native proteins, events that can be linked to a measurable response.

Examples of such biological responses include, but are not limited to, the following: the ability to survive in the absence of a limiting nutrient in specifically engineered yeast cells (Pausch, *Trends in Biotechnology*, 1997, 15, 487-494); changes in intracellular Ca^{2+} concentration as measured by fluorescent dyes (Murphy, *et al.*, *Cur. Opinion Drug Disc. Dev.*,

1998, 1, 192-199). Fluorescence changes can also be used to monitor ligand-induced changes in membrane potential or intracellular pH; an automated system suitable for HTS has been described for these purposes (Schroeder, *et al.*, *J. Biomolecular Screening*, 1996, 1, 75-80).

Melanophores prepared from *Xenopus laevis* show a ligand-dependent change in pigment

5 organization in response to heterologous GPCR activation; this response is adaptable to HTS formats (Jayawickreme *et al.*, *Cur. Opinion Biotechnology*, 1997, 8, 629-634). Assays are also available for the measurement of common second messengers, including cAMP, phosphoinositides and arachidonic acid, but these are not generally preferred for HTS.

Preferred methods of HTS employing these receptors include permanently transfected
10 CHO cells, in which agonists and antagonists can be identified by the ability to specifically alter the binding of GTP γ [³⁵S] in membranes prepared from these cells. In another embodiment of the invention, permanently transfected CHO cells could be used for the preparation of membranes which contain significant amounts of the recombinant receptor proteins; these membrane preparations would then be used in receptor binding assays, employing the radiolabelled ligand
15 specific for the particular receptor. Alternatively, a functional assay, such as fluorescent monitoring of ligand-induced changes in internal Ca²⁺ concentration or membrane potential in permanently transfected CHO cells containing each of these receptors individually or in combination would be preferred for HTS. Equally preferred would be an alternative type of mammalian cell, such as HEK293 or COS cells, in similar formats. More preferred would be
20 permanently transfected insect cell lines, such as *Drosophila* S2 cells. Even more preferred would be recombinant yeast cells expressing the *Drosophila melanogaster* receptors in HTS formats well known to those skilled in the art (*e.g.*, Pausch, *Trends in Biotechnology*, 1997, 15, 487-494).

The invention contemplates a multitude of assays to screen and identify inhibitors of
25 ligand binding to nGPCR-x receptors. In one example, the nGPCR-x receptor is immobilized and interaction with a binding partner is assessed in the presence and absence of a candidate modulator such as an inhibitor compound. In another example, interaction between the nGPCR-x receptor and its binding partner is assessed in a solution assay, both in the presence and absence of a candidate inhibitor compound. In either assay, an inhibitor is identified as a
30 compound that decreases binding between the nGPCR-x receptor and its binding partner. Following identification of compounds that inhibit ligand binding to nGPCR-x receptors, such compounds can be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate their activity. Another contemplated assay involves a variation of

the dihybrid assay wherein an inhibitor of protein/protein interactions is identified by detection of a positive signal in a transformed or transfected host cell, as described in PCT publication number WO 95/20652, published August 3, 1995.

Candidate modulators contemplated by the invention include compounds selected from
5 libraries of either potential activators or potential inhibitors. There are a number of different libraries used for the identification of small molecule modulators, including: (1) chemical libraries, (2) natural product libraries, and (3) combinatorial libraries comprised of random peptides, oligonucleotides or organic molecules. Chemical libraries consist of random chemical structures, some of which are analogs of known compounds or analogs of compounds that have
10 been identified as "hits" or "leads" in other drug discovery screens, some of which are derived from natural products, and some of which arise from non-directed synthetic organic chemistry. Natural product libraries are collections of microorganisms, animals, plants, or marine organisms which are used to create mixtures for screening by: (1) fermentation and extraction of broths from soil, plant or marine microorganisms or (2) extraction of plants or marine
15 organisms. Natural product libraries include polyketides, non-ribosomal peptides, and variants (non-naturally occurring) thereof. For a review, see *Science* 282:63-68 (1998). Combinatorial libraries are composed of large numbers of peptides, oligonucleotides, or organic compounds as a mixture. These libraries are relatively easy to prepare by traditional automated synthesis methods, PCR, cloning, or proprietary synthetic methods. Of particular interest are non-peptide
20 combinatorial libraries. Still other libraries of interest include peptide, protein, peptidomimetic, multiparallel synthetic collection, recombinatorial, and polypeptide libraries. For a review of combinatorial chemistry and libraries created therefrom, see Myers, *Curr. Opin. Biotechnol.* 8:701-707 (1997). Identification of modulators through use of the various libraries described herein permits modification of the candidate "hit" (or "lead") to optimize the capacity of the
25 "hit" to modulate activity.

Still other candidate inhibitors contemplated by the invention can be designed and include soluble forms of binding partners, as well as such binding partners as chimeric, or fusion, proteins. A "binding partner" as used herein broadly encompasses non-peptide modulators, as well as such peptide modulators as neuropeptides other than natural ligands,
30 antibodies, antibody fragments, and modified compounds comprising antibody domains that are immunospecific for the expression product of the identified nGPCR-x gene.

The polypeptides of the invention are employed as a research tool for identification, characterization and purification of interacting, regulatory proteins. Appropriate labels are

incorporated into the polypeptides of the invention by various methods known in the art and the polypeptides are used to capture interacting molecules. For example, molecules are incubated with the labeled polypeptides, washed to remove unbound polypeptides, and the polypeptide complex is quantified. Data obtained using different concentrations of polypeptide are used to
5 calculate values for the number, affinity, and association of polypeptide with the protein complex.

Labeled polypeptides are also useful as reagents for the purification of molecules with which the polypeptide interacts including, but not limited to, inhibitors. In one embodiment of affinity purification, a polypeptide is covalently coupled to a chromatography column. Cells and
10 their membranes are extracted, and various cellular subcomponents are passed over the column. Molecules bind to the column by virtue of their affinity to the polypeptide. The polypeptide-complex is recovered from the column, dissociated and the recovered molecule is subjected to protein sequencing. This amino acid sequence is then used to identify the captured molecule or to design degenerate oligonucleotides for cloning the corresponding gene from an appropriate
15 cDNA library.

Alternatively, compounds may be identified which exhibit similar properties to the ligand for the nGPCR-x of the invention, but which are smaller and exhibit a longer half time than the endogenous ligand in a human or animal body. When an organic compound is designed, a molecule according to the invention is used as a "lead" compound. The design of mimetics to
20 known pharmaceutically active compounds is a well-known approach in the development of pharmaceuticals based on such "lead" compounds. Mimetic design, synthesis and testing are generally used to avoid randomly screening a large number of molecules for a target property. Furthermore, structural data deriving from the analysis of the deduced amino acid sequences encoded by the DNAs of the present invention are useful to design new drugs, more specific and
25 therefore with a higher pharmacological potency.

Comparison of the protein sequence of the present invention with the sequences present in all the available databases showed a significant homology with the transmembrane portion of G protein coupled receptors. Accordingly, computer modeling can be used to develop a putative tertiary structure of the proteins of the invention based on the available information of the
30 transmembrane domain of other proteins. Thus, novel ligands based on the predicted structure of nGPCR-x can be designed.

In a particular embodiment, the novel molecules identified by the screening methods according to the invention are low molecular weight organic molecules, in which case a

composition or pharmaceutical composition can be prepared thereof for oral intake, such as in tablets. The compositions, or pharmaceutical compositions, comprising the nucleic acid molecules, vectors, polypeptides, antibodies and compounds identified by the screening methods described herein, can be prepared for any route of administration including, but not limited to, oral, intravenous, cutaneous, subcutaneous, nasal, intramuscular or intraperitoneal. The nature of the carrier or other ingredients will depend on the specific route of administration and particular embodiment of the invention to be administered. Examples of techniques and protocols that are useful in this context are, *inter alia*, found in Remington's Pharmaceutical Sciences, 16th edition, Osol, A (ed.), 1980, which is incorporated herein by reference in its entirety.

The dosage of these low molecular weight compounds will depend on the disease state or condition to be treated and other clinical factors such as weight and condition of the human or animal and the route of administration of the compound. For treating human or animals, between approximately 0.5 mg/kg of body weight to 500 mg/kg of body weight of the compound can be administered. Therapy is typically administered at lower dosages and is continued until the desired therapeutic outcome is observed.

The present compounds and methods, including nucleic acid molecules, polypeptides, antibodies, compounds identified by the screening methods described herein, have a variety of pharmaceutical applications and may be used, for example, to treat or prevent unregulated cellular growth, such as cancer cell and tumor growth. In a particular embodiment, the present molecules are used in gene therapy. For a review of gene therapy procedures, see *e.g.* Anderson, *Science*, 1992, 256, 808-813, which is incorporated herein by reference in its entirety.

The present invention also encompasses a method of agonizing (stimulating) or antagonizing a nGPCR-x natural binding partner associated activity in a mammal comprising administering to said mammal an agonist or antagonist to one of the above disclosed polypeptides in an amount sufficient to effect said agonism or antagonism. One embodiment of the present invention, then, is a method of treating diseases in a mammal with an agonist or antagonist of the protein of the present invention comprises administering the agonist or antagonist to a mammal in an amount sufficient to agonize or antagonize nGPCR-x-associated functions.

In an effort to discover novel treatments for diseases, biomedical researchers and chemists have designed, synthesized, and tested molecules that modulate the function of G protein coupled receptors. Some small organic molecules form a class of compounds that modulate the function of G protein coupled receptors.

Exemplary diseases and conditions amenable to treatment based on the present invention include, but are not limited to, thyroid disorders (*e.g.* thyreotoxicosis, myxoedema); renal failure; inflammatory conditions (*e.g.*, Crohn's disease); diseases related to cell differentiation and homeostasis; rheumatoid arthritis; autoimmune disorders; movement disorders; CNS disorders (*e.g.*, pain including migraine; stroke; psychotic and neurological disorders, including anxiety, mental disorder, manic depression, anxiety, generalized anxiety disorder, post-traumatic-stress disorder, Schizophrenia, depression, bipolar disorder, delirium, dementia, severe mental retardation; dyskinesias, such as Huntington's disease or Tourette's Syndrome; attention disorders including ADD and ADHD, and degenerative disorders such as Parkinson's, Alzheimer's; movement disorders, including ataxias, supranuclear palsy, *etc.*); infections, such as viral infections caused by HIV-1 or HIV-2; metabolic and cardiovascular diseases and disorders (*e.g.*, type 2 diabetes, impaired glucose tolerance, dyslipidemia, obesity, anorexia, hypotension, hypertension, thrombosis, myocardial infarction, cardiomyopathies, atherosclerosis, *etc.*); proliferative diseases and cancers (*e.g.*, different cancers such as breast, colon, lung, *etc.*, and hyperproliferative disorders such as psoriasis, prostate hyperplasia, *etc.*); hormonal disorders (*e.g.*, male/female hormonal replacement, polycystic ovarian syndrome, alopecia, *etc.*); sexual dysfunction, among others.

Methods of determining the dosages of compounds to be administered to a patient and modes of administering compounds to an organism are disclosed in International patent publication number WO 96/22976, published August 1 1996, both of which are incorporated herein by reference in their entirety, including any drawings, figures or tables. Those skilled in the art will appreciate that such descriptions are applicable to the present invention and can be easily adapted to it.

The proper dosage depends on various factors such as the type of disease being treated, the particular composition being used and the size and physiological condition of the patient, including such factors as, for example, weight, age, sex, disease state, *etc.* Therapeutically effective doses for the compounds described herein can be estimated initially from cell culture and animal models. For example, a dose can be formulated in animal models to achieve a circulating concentration range that initially takes into account the IC_{50} as determined in cell culture assays. The animal model data can be used to more accurately determine useful doses in humans.

Plasma half-life and biodistribution of the drug and metabolites in the plasma, tumors and major organs can also be determined to facilitate the selection of drugs most appropriate to

inhibit a disorder. Such measurements can be carried out. For example, HPLC analysis can be performed on the plasma of animals treated with the drug and the location of radiolabeled compounds can be determined using detection methods such as X-ray, CAT scan and MRI. Compounds that show potent inhibitory activity in the screening assays, but have poor pharmacokinetic characteristics, can be optimized by altering the chemical structure and retesting. In this regard, compounds displaying good pharmacokinetic characteristics can be used as a model.

Toxicity studies can also be carried out by measuring the blood cell composition. For example, toxicity studies can be carried out in a suitable animal model as follows: 1) the compound is administered to mice (an untreated control mouse should also be used); 2) blood samples are periodically obtained via the tail vein from one mouse in each treatment group; and 3) the samples are analyzed for red and white blood cell counts, blood cell composition and the percent of lymphocytes versus polymorphonuclear cells. A comparison of results for each dosing regime with the controls indicates if toxicity is present.

At the termination of each toxicity study, further studies can be carried out by sacrificing the animals (preferably, in accordance with the American Veterinary Medical Association guidelines Report of the American Veterinary Medical Assoc. Panel on Euthanasia, Journal of American Veterinary Medical Assoc., 202:229-249, 1993). Representative animals from each treatment group can then be examined by gross necropsy for immediate evidence of metastasis, unusual illness or toxicity. Gross abnormalities in tissue are noted and tissues are examined histologically. Compounds causing a reduction in body weight or blood components are less preferred, as are compounds having an adverse effect on major organs. In general, the greater the adverse effect the less preferred the compound.

For the treatment of many diseases, the expected daily dose of a hydrophobic pharmaceutical agent is between 1 to 500 mg/day, preferably 1 to 250 mg/day, and most preferably 1 to 50 mg/day. Drugs can be delivered less frequently provided plasma levels of the active moiety are sufficient to maintain therapeutic effectiveness. Plasma levels should reflect the potency of the drug. Generally, the more potent the compound the lower the plasma levels necessary to achieve efficacy.

Sequences selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:67 will, as detailed above, enable screening the endogenous neurotransmitters/hormones/ligands which activate, agonize, or antagonize nGPCR-x and for compounds with potential utility in treating disorders including, but not limited to, thyroid disorders (*e.g.* thyreotoxicosis, myxoedema); renal failure; inflammatory conditions (*e.g.*, Crohn's disease); diseases related to cell

differentiation and homeostasis; rheumatoid arthritis; autoimmune disorders; movement disorders; CNS disorders (*e.g.*, pain including migraine; stroke; psychotic and neurological disorders, including anxiety, mental disorder, manic depression, anxiety, generalized anxiety disorder, post-traumatic-stress disorder, Schizophrenia, depression, bipolar disorder, delirium, dementia, severe mental retardation; dyskinesias, such as Huntington's disease or Tourette's Syndrome; attention disorders including ADD and ADHD, and degenerative disorders such as Parkinson's, Alzheimer's; movement disorders, including ataxias, supranuclear palsy, *etc.*); infections, such as viral infections caused by HIV-1 or HIV-2; metabolic and cardiovascular diseases and disorders (*e.g.*, type 2 diabetes, impaired glucose tolerance, dyslipidemia, obesity, anorexia, hypotension, hypertension, thrombosis, myocardial infarction, cardiomyopathies, atherosclerosis, *etc.*); proliferative diseases and cancers (*e.g.*, different cancers such as breast, colon, lung, *etc.*, and hyperproliferative disorders such as psoriasis, prostate hyperplasia, *etc.*); hormonal disorders (*e.g.*, male/female hormonal replacement, polycystic ovarian syndrome, alopecia, *etc.*); sexual dysfunction, among others.

For example, nGPCR-x may be useful in the treatment of respiratory ailments such as asthma, where T cells are implicated by the disease. Contraction of airway smooth muscle is stimulated by thrombin. Cicala *et al* (1999) Br J Pharmacol 126:478-484. Additionally, in bronchiolitis obliterans, it has been noted that activation of thrombin receptors may be deleterious. Hauck *et al.* (1999) Am J Physiol 277:L22-L29. Furthermore, mast cells have also been shown to have thrombin receptors. Cirino *et al* (1996) J Exp Med 183:821-827. nGPCR-x may also be useful in remodeling of airway structures in chronic pulmonary inflammation via stimulation of fibroblast procollagen synthesis. See, *e.g.*, Chambers *et al.* (1998) Biochem J 333:121-127; Trejo *et al.* (1996) J Biol Chem 271:21536-21541.

In another example, increased release of sCD40L and expression of CD40L by T cells after activation of thrombin receptors suggests that nGPCR-x may be useful in the treatment of unstable angina due to the role of T cells and inflammation. See Aukrust *et al.* (1999) Circulation 100:614-620.

A further example is the treatment of inflammatory diseases, such as psoriasis, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, and thyroiditis. Due to the tissue expression profile of nGPCR-x, inhibition of thrombin receptors may be beneficial for these diseases. See, *e.g.*, Morris *et al.* (1996) Ann Rheum Dis 55:841-843. In addition to T cells, NK cells and monocytes are also critical cell types which contribute to the pathogenesis of these

diseases. See, e.g., Naldini & Carney (1996) *Cell Immunol* 172:35-42; Hoffman & Cooper (1995) *Blood Cells Mol Dis* 21:156-167; Colotta *et al.* (1994) *Am J Pathol* 144:975-985.

Expression of nGPCR-x in bone marrow and spleen may suggest that it may play a role in the proliferation of hematopoietic progenitor cells. See DiCuccio *et al.* (1996) *Exp Hematol* 24:914-918.

As another example, nGPCR-x may be useful in the treatment of acute and/or traumatic brain injury. Astrocytes have been demonstrated to express thrombin receptors. Activation of thrombin receptors may be involved in astrogliosis following brain injury. Therefore, inhibition of receptor activity may be beneficial for limiting neuroinflammation. Scar formation mediated by astrocytes may also be limited by inhibiting thrombin receptors. See, e.g., Pindon *et al.* (1998) *Eur J Biochem* 255:766-774; Uhl & Reiser. (1997) *Glia* 21:361-369; Grabham & Cunningham (1995) *J Neurochem* 64:583-591.

nGPCR-x receptor activation may mediate neuronal and astrocyte apoptosis and prevention of neurite outgrowth. Inhibition would be beneficial in both chronic and acute brain injury. See, e.g., Donovan *et al.* (1997) *J Neurosci* 17:5316-5326; Turgeon *et al.* (1998) *J Neurosci* 18:6882-6891; Smith-Swintosky *et al.* (1997) *J Neurochem* 69:1890-1896; Gill *et al.* (1998) *Brain Res* 797:321-327; Suidan *et al.* (1996) *Semin Thromb Hemost* 22:125-133.

The attached Sequence Listing contains the sequences of the polynucleotides and polypeptides of the invention and is incorporated herein by reference in its entirety.

As one skilled in the art knows, numerous GPCRs have been detected in brain tissue indicating that these n-GPCR-x proteins are neuroreceptors. The identification of modulators such as agonists and antagonists is therefore useful for the identification of compounds useful to treat neurological diseases and psychiatric disorders. Such neurological diseases and disorders, including but are not limited to, mental disorder, affective disorders, ADHD/ADD, and neural disorders such as Alzheimer's disease, Parkinson's disease, migraine, schizophrenia, and senile dementia as well as depression, anxiety, bipolar disease, epilepsy, neuritis, neurasthenia, neuropathy, neuroses, and the like.

Methods of Screening Human Subjects

Thus in yet another embodiment, the invention provides genetic screening procedures that entail analyzing a person's genome — in particular their alleles for GPCRs of the invention - - to determine whether the individual possesses a genetic characteristic found in other individuals that are considered to be afflicted with, or at risk for, developing a mental disorder or disease of the brain that is suspected of having a hereditary component. For example, in one

embodiment, the invention provides a method for determining a potential for developing a disorder affecting the brain in a human subject comprising the steps of analyzing the coding sequence of one or more GPCR genes from the human subject; and determining development potential for the disorder in said human subject from the analyzing step.

5 More particularly, the invention provides a method of screening a human subject to diagnose a disorder affecting the brain or genetic predisposition therefor, comprising the steps of: (a) assaying nucleic acid of a human subject to determine a presence or an absence of a mutation altering the amino acid sequence, expression, or biological activity of at least one seven transmembrane receptor that is expressed in the brain, wherein the nucleic acid
10 corresponds to the gene encoding the seven transmembrane receptor; and (b) diagnosing the disorder or predisposition from the presence or absence of said mutation, wherein the presence of a mutation altering the amino acid sequence, expression, or biological activity of allele in the nucleic acid correlates with an increased risk of developing the disorder. In preferred variations, the seven transmembrane receptor is nGPCR-x, or an allelic variant thereof, and the disease is
15 mental disorder.

By "human subject" is meant any human being, human embryo, or human fetus. It will be apparent that methods of the present invention will be of particular interest to individuals that have themselves been diagnosed with a disorder affecting the brain or have relatives that have been diagnosed with a disorder affecting the brain.

20 By "screening for an increased risk" is meant determination of whether a genetic variation exists in the human subject that correlates with a greater likelihood of developing a disorder affecting the brain than exists for the human population as a whole, or for a relevant racial or ethnic human sub-population to which the individual belongs. Both positive and negative determinations (i.e., determinations that a genetic predisposition marker is present or is
25 absent) are intended to fall within the scope of screening methods of the invention. In preferred embodiments, the presence of a mutation altering the sequence or expression of at least one nGPCR-x seven transmembrane receptor allele in the nucleic acid is correlated with an increased risk of developing mental disorder, whereas the absence of such a mutation is reported as a negative determination.

30 The "assaying" step of the invention may involve any techniques available for analyzing nucleic acid to determine its characteristics, including but not limited to well-known techniques such as single-strand conformation polymorphism analysis (SSCP) (Orita *et al.*, *Proc Natl. Acad. Sci. USA*, 86: 2766-2770 (1989)); heteroduplex analysis (White *et al.*, *Genomics*, 12: 301-

306 (1992)); denaturing gradient gel electrophoresis analysis (Fischer *et al.*, *Proc. Natl. Acad. Sci. USA*, 80: 1579-1583 (1983); and Riesner *et al.*, *Electrophoresis*, 10: 377-389 (1989)); DNA sequencing; RNase cleavage (Myers *et al.*, *Science*, 230: 1242-1246 (1985)); chemical cleavage of mismatch techniques (Rowley *et al.*, *Genomics*, 30: 574-582 (1995); and Roberts *et al.*, *Nucl. Acids Res.*, 25: 3377-3378 (1997)); restriction fragment length polymorphism analysis; single nucleotide primer extension analysis (Shumaker *et al.*, *Hum. Mutat.*, 7: 346-354 (1996); and Pastinen *et al.*, *Genome Res.*, 7: 606-614 (1997)); 5' nuclease assays (Pease *et al.*, *Proc. Natl. Acad. Sci. USA*, 91:5022-5026 (1994)); DNA Microchip analysis (Ramsay, G., *Nature Biotechnology*, 16: 40-48 (1999); and Chee *et al.*, U.S. Patent No. 5,837,832); and ligase chain reaction (Whiteley *et al.*, U.S. Patent No. 5,521,065). (See generally, Schafer and Hawkins, *Nature Biotechnology*, 16: 33-39 (1998).) All of the foregoing documents are hereby incorporated herein by reference in their entirety.

Thus, in one preferred embodiment involving screening nGPCR-x, for example, the assaying step comprises at least one procedure selected from the group consisting of: (a) determining a nucleotide sequence of at least one codon of at least one nGPCR-x allele of the human subject; (b) performing a hybridization assay to determine whether nucleic acid from the human subject has a nucleotide sequence identical to or different from one or more reference sequences; (c) performing a polynucleotide migration assay to determine whether nucleic acid from the human subject has a nucleotide sequence identical to or different from one or more reference sequences; and (d) performing a restriction endonuclease digestion to determine whether nucleic acid from the human subject has a nucleotide sequence identical to or different from one or more reference sequences.

In a highly preferred embodiment, the assaying involves sequencing of nucleic acid to determine nucleotide sequence thereof, using any available sequencing technique. (See, *e.g.*, Sanger *et al.*, *Proc. Natl. Acad. Sci. (USA)*, 74: 5463-5467 (1977) (dideoxy chain termination method); Mirzabekov, *TIBTECH*, 12: 27-32 (1994) (sequencing by hybridization); Drmanac *et al.*, *Nature Biotechnology*, 16: 54-58 (1998); U.S. Patent No. 5,202,231; and *Science*, 260: 1649-1652 (1993) (sequencing by hybridization); Kieleczawa *et al.*, *Science*, 258: 1787-1791 (1992) (sequencing by primer walking); (Douglas *et al.*, *Biotechniques*, 14: 824-828 (1993) (Direct sequencing of PCR products); and Akane *et al.*, *Biotechniques* 16: 238-241 (1994); Maxam and Gilbert, *Meth. Enzymol.*, 65: 499-560 (1977) (chemical termination sequencing), all incorporated herein by reference in its entirety). The analysis may entail sequencing of the entire nGPCR gene genomic DNA sequence, or portions thereof; or sequencing of the entire seven

transmembrane receptor coding sequence or portions thereof. In some circumstances, the analysis may involve a determination of whether an individual possesses a particular allelic variant, in which case sequencing of only a small portion of nucleic acid -- enough to determine the sequence of a particular codon characterizing the allelic variant -- is sufficient. This approach is appropriate, for example, when assaying to determine whether one family member inherited the same allelic variant that has been previously characterized for another family member, or, more generally, whether a person's genome contains an allelic variant that has been previously characterized and correlated with a mental disorder having a heritable component.

In another highly preferred embodiment, the assaying step comprises performing a hybridization assay to determine whether nucleic acid from the human subject has a nucleotide sequence identical to or different from one or more reference sequences. In a preferred embodiment, the hybridization involves a determination of whether nucleic acid derived from the human subject will hybridize with one or more oligonucleotides, wherein the oligonucleotides have nucleotide sequences that correspond identically to a portion of the GPCR gene sequence taught herein, such as the nGPCR-x coding sequence, or that correspond identically except for one mismatch. The hybridization conditions are selected to differentiate between perfect sequence complementarity and imperfect matches differing by one or more bases. Such hybridization experiments thereby can provide single nucleotide polymorphism sequence information about the nucleic acid from the human subject, by virtue of knowing the sequences of the oligonucleotides used in the experiments.

Several of the techniques outlined above involve an analysis wherein one performs a polynucleotide migration assay, *e.g.*, on a polyacrylamide electrophoresis gel (or in a capillary electrophoresis system), under denaturing or non-denaturing conditions. Nucleic acid derived from the human subject is subjected to gel electrophoresis, usually adjacent to (or co-loaded with) one or more reference nucleic acids. The nucleic acid from the human subject and the reference sequence(s) are subjected to similar chemical or enzymatic treatments and then electrophoresed under conditions whereby the polynucleotides will show a differential migration pattern, unless they contain identical sequences. (See generally Ausubel *et al.* (eds.), *Current Protocols in Molecular Biology*, New York: John Wiley & Sons, Inc. (1987-1999); and Sambrook *et al.*, (eds.), *Molecular Cloning, A Laboratory Manual*, Cold Spring Harbor, New York: Cold Spring Harbor Laboratory Press (1989), both incorporated herein by reference in their entirety).

In the context of assaying, the term “nucleic acid of a human subject” is intended to include nucleic acid obtained directly from the human subject (*e.g.*, DNA or RNA obtained from a biological sample such as a blood, tissue, or other cell or fluid sample); and also nucleic acid derived from nucleic acid obtained directly from the human subject. By way of non-limiting examples, well known procedures exist for creating cDNA that is complementary to RNA derived from a biological sample from a human subject, and for amplifying (*e.g.*, via polymerase chain reaction (PCR)) DNA or RNA derived from a biological sample obtained from a human subject. Any such derived polynucleotide which retains relevant nucleotide sequence information of the human subject’s own DNA/RNA is intended to fall within the definition of “nucleic acid of a human subject” for the purposes of the present invention.

In the context of assaying, the term “mutation” includes addition, deletion, and/or substitution of one or more nucleotides in the GPCR gene sequence (*e.g.*, as compared to the seven transmembrane receptor-encoding sequences) and other polymorphisms that occur in introns (where introns exist) and that are identifiable via sequencing, restriction fragment length polymorphism, or other techniques. The various activity examples provided herein permit determination of whether a mutation modulates activity of the relevant receptor in the presence or absence of various test substances.

In a related embodiment, the invention provides methods of screening a person’s genotype with respect to GPCRs of the invention, and correlating such genotypes with diagnoses for disease or with predisposition for disease (for genetic counseling). For example, the invention provides a method of screening for an nGPCR-x hereditary mental disorder genotype in a human patient, comprising the steps of: (a) providing a biological sample comprising nucleic acid from the patient, the nucleic acid including sequences corresponding to said patient’s nGPCR-x alleles; (b) analyzing the nucleic acid for the presence of a mutation or mutations; (c) determining an nGPCR-x genotype from the analyzing step; and (d) correlating the presence of a mutation in an nGPCR-x allele with a hereditary mental disorder genotype. In a preferred embodiment, the biological sample is a cell sample containing human cells that contain genomic DNA of the human subject. The analyzing can be performed analogously to the assaying described in preceding paragraphs. For example, the analyzing comprises sequencing a portion of the nucleic acid (*e.g.*, DNA or RNA), the portion comprising at least one codon of the nGPCR-x alleles.

Although more time consuming and expensive than methods involving nucleic acid analysis, the invention also may be practiced by assaying protein of a human subject to

determine the presence or absence of an amino acid sequence variation in GPCR protein from the human subject. Such protein analyses may be performed, *e.g.*, by fragmenting GPCR protein via chemical or enzymatic methods and sequencing the resultant peptides; or by Western analyses using an antibody having specificity for a particular allelic variant of the GPCR.

5 The invention also provides materials that are useful for performing methods of the invention. For example, the present invention provides oligonucleotides useful as probes in the many analyzing techniques described above. In general, such oligonucleotide probes comprise 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 nucleotides that have a
10 sequence that is identical, or exactly complementary, to a portion of a human GPCR gene sequence taught herein (or allelic variant thereof), or that is identical or exactly complementary except for one nucleotide substitution. In a preferred embodiment, the oligonucleotides have a sequence that corresponds in the foregoing manner to a human GPCR coding sequence taught herein. In one variation, an oligonucleotide probe of the invention is purified and isolated. In
15 another variation, the oligonucleotide probe is labeled, *e.g.*, with a radioisotope, chromophore, or fluorophore. In yet another variation, the probe is covalently attached to a solid support. (See generally Ausubel *et al.* and Sambrook *et al.*, *supra*.)

 In a related embodiment, the invention provides kits comprising reagents that are useful for practicing methods of the invention. For example, the invention provides a kit for screening
20 a human subject to diagnose a mental disorder or a genetic predisposition therefor, comprising, in association: (a) an oligonucleotide useful as a probe for identifying polymorphisms in a human nGPCR-x seven transmembrane receptor gene, the oligonucleotide comprising 6-50 nucleotides that have a sequence that is identical or exactly complementary to a portion of a human nGPCR-x gene sequence or nGPCR-x coding sequence, except for one sequence
25 difference selected from the group consisting of a nucleotide addition, a nucleotide deletion, or nucleotide substitution; and (b) a media packaged with the oligonucleotide containing information identifying polymorphisms identifiable with the probe that correlate with mental disorder or a genetic predisposition therefor. Exemplary information-containing media include printed paper package inserts or packaging labels; and magnetic and optical storage media that
30 are readable by computers or machines used by practitioners who perform genetic screening and counseling services. The practitioner uses the information provided in the media to correlate the results of the analysis with the oligonucleotide with a diagnosis. In a preferred variation, the oligonucleotide is labeled.

In still another embodiment, the invention provides methods of identifying those allelic variants of GPCRs of the invention that correlate with mental disorders. For example, the invention provides a method of identifying a seven transmembrane allelic variant that correlates with a mental disorder, comprising steps of: (a) providing a biological sample comprising nucleic acid from a human patient diagnosed with a mental disorder, or from the patient's genetic progenitors or progeny; (b) analyzing the nucleic acid for the presence of a mutation or mutations in at least one seven transmembrane receptor that is expressed in the brain, wherein the nucleic acid includes sequence corresponding to the gene or genes encoding the at least one seven transmembrane receptor; (c) determining a genotype for the patient for the at least one seven transmembrane receptor from said analyzing step; and (d) identifying an allelic variant that correlates with the mental disorder from the determining step. To expedite this process, it may be desirable to perform linkage studies in the patients (and possibly their families) to correlate chromosomal markers with disease states. The chromosomal localization data provided herein facilitates identifying an involved GPCR with a chromosomal marker.

The foregoing method can be performed to correlate GPCRs of the invention to a number of disorders having hereditary components that are causative or that predispose persons to the disorder. For example, in one preferred variation, the disorder is a mental disorder, and the at least one seven transmembrane receptor comprises nGPCR-x or an allelic variant thereof.

Also contemplated as part of the invention are polynucleotides that comprise the allelic variant sequences identified by such methods, and polypeptides encoded by the allelic variant sequences, and oligonucleotide and oligopeptide fragments thereof that embody the mutations that have been identified. Such materials are useful in *in vitro* cell-free and cell-based assays for identifying lead compounds and therapeutics for treatment of the disorders. For example, the variants are used in activity assays, binding assays, and assays to screen for activity modulators described herein. In one preferred embodiment, the invention provides a purified and isolated polynucleotide comprising a nucleotide sequence encoding a nGPCR-x receptor allelic variant identified according to the methods described above; and an oligonucleotide that comprises the sequences that differentiate the allelic variant from the nGPCR-x sequences. The invention also provides a vector comprising the polynucleotide (preferably an expression vector); and a host cell transformed or transfected with the polynucleotide or vector. The invention also provides an isolated cell line that is expressing the allelic variant GPCR polypeptide; purified cell membranes from such cells; purified polypeptide; and synthetic peptides that embody the allelic variation amino acid sequence. In one particular embodiment, the invention provides a purified

polynucleotide comprising a nucleotide sequence encoding a nGPCR-x seven transmembrane receptor protein of a human that is affected with a mental disorder; wherein said polynucleotide hybridizes to the complement of nGPCR-x under the following hybridization conditions: (a) hybridization for 16 hours at 42C in a hybridization solution comprising 50% formamide, 1% SDS, 1 M NaCl, 10% dextran sulfate and (b) washing 2 times for 30 minutes at 60C in a wash solution comprising 0.1x SSC and 1% SDS; and wherein the polynucleotide encodes a nGPCR-x amino acid sequence that differs by at least one residue.

An exemplary assay for using the allelic variants is a method for identifying a modulator of nGPCR-x biological activity, comprising the steps of: (a) contacting a cell expressing the allelic variant in the presence and in the absence of a putative modulator compound; (b) measuring nGPCR-x biological activity in the cell; and (c) identifying a putative modulator compound in view of decreased or increased nGPCR-x biological activity in the presence versus absence of the putative modulator.

Additional features of the invention will be apparent from the following Examples.

Example 1 is actual, while the remaining Examples are prophetic. Additional features and variations of the invention will be apparent to those skilled in the art from the entirety of this application, including the detailed description, and all such features are intended as aspects of the invention. Likewise, features of the invention described herein can be re-combined into additional embodiments that also are intended as aspects of the invention, irrespective of whether the combination of features is specifically mentioned above as an aspect or embodiment of the invention. Also, only such limitations which are described herein as critical to the invention should be viewed as such; variations of the invention lacking limitations which have not been described herein as critical are intended as aspects of the invention.

EXAMPLES

Example 1: Identification of nGPCR-x

A. Database search

The Celera database was searched using known GPCR receptors as query sequences to find patterns suggestive of novel G protein-coupled receptors. Positive hits were further analyzed with the GCG program BLAST to determine which ones were the most likely candidates to encode G protein-coupled receptors, using the standard (default) alignment produced by BLAST as a guide.

Briefly, the BLAST algorithm, which stands for Basic Local Alignment Search Tool is suitable for determining sequence similarity (Altschul *et al.*, J. Mol. Biol., 1990, 215, 403-410,

which is incorporated herein by reference in its entirety). Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information through the world wide web of the Internet (ncbi.nlm.nih.gov/). This algorithm involves first identifying high scoring sequence pair (HSPs) by identifying short words of length W in the query sequence that either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul et al., supra). These initial neighbourhood word hits act as seeds for initiating searches to find HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Extension for the word hits in each direction are halted when: 1) the cumulative alignment score falls off by the quantity X from its maximum achieved value; 2) the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or 3) the end of either sequence is reached. The Blast algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The Blast program uses as defaults a word length (W) of 11, the BLOSUM62 scoring matrix (see Henikoff et al., Proc. Natl. Acad. Sci. USA, 1992, 89, 10915-10919, which is incorporated herein by reference in its entirety) alignments (B) of 50, expectation (E) of 10, M=5, N=4, and a comparison of both strands.

The BLAST algorithm (Karlin *et al.*, Proc. Natl. Acad. Sci. USA, 1993, 90, 5873-5787, which is incorporated herein by reference in its entirety) and Gapped BLAST perform a statistical analysis of the similarity between two sequences. One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a GPCR gene or cDNA if the smallest sum probability in comparison of the test nucleic acid to a GPCR nucleic acid is less than about 1, preferably less than about 0.1, more preferably less than about 0.01, and most preferably less than about 0.001.

Homology searches are performed with the program BLAST version 2.08. A collection of about 200 to about 350 query amino acid sequences derived from GPCRs was used to search the genomic DNA sequence using TBLASTN and alignments with an E-value lower than 0.01 were collected from each BLAST search. The amino acid sequences have been edited to remove regions in the sequence that produce non-significant alignments with proteins that are not related to GPCRs.

Multiple query sequences may have a significant alignment to the same genomic region, although each alignment may not cover exactly the same DNA region. A procedure is used to determine the region of maximum common overlap between the alignments from several query sequences. This region is called the consensus DNA region. The procedure for determining this
5 consensus involves the automatic parsing of the BLAST output files using the program MSPcrunch to produce a tabular report. From this tabular report the start and end of each alignment in the genomic DNA is extracted. This information is used by a PERL script to derive the maximum common overlap. These regions are reported in the form of a unique sequence identifier, a start and the end position in the sequence. The sequences defined by these regions
10 were extracted from the original genomic sequence file using the program fetchdb.

The consensus regions are assembled into a non-redundant set by using the program phrap. After assembly with phrap a set of contigs and singletons were defined as candidate DNA regions coding for nGPCRs. These sequences were then submitted for further sequence analysis.

Further sequence analysis involves the removal of sequences previously isolated and
15 removal of sequences that are related to olfactory GPCRs. The transmembrane regions for the sequences that remained were determined using a FORTRAN computer program called "tmrest.all" (Parodi *et al.*, Comput.Appl.Biosci. 5:527-535(1994)). Only sequences that contained transmembrane regions in a pattern found in GPCRs were retained.

nGPCR-x cDNAs were sequenced directly using an ABI377 fluorescence-based
20 sequencer (Perkin-Elmer/Applied Biosystems Division, PE/ABD, Foster City, CA) and the ABI PRISMTM Ready Dye-Deoxy Terminator kit with Taq FSTM polymerase. Each ABI cycle sequencing reaction contained about 0.5 µg of plasmid DNA. Cycle-sequencing was performed using an initial denaturation at 98C for 1 minute, followed by 50 cycles using the following parameters: 98C for 30 seconds, annealing at 50C for 30 seconds, and extension at 60C for 4
25 minutes. Temperature cycles and times were controlled by a Perkin-Elmer 9600 thermocycler. Extension products were purified using CentriflexTM gel filtration cartridges (Advanced Genetic Technologies Corp., Gaithersburg, MD). Each reaction product was loaded by pipette onto the column, which is then centrifuged in a swinging bucket centrifuge (Sorvall model RT6000B tabletop centrifuge) at 1500 x g for 4 minutes at room temperature. Column-purified samples
30 were dried under vacuum for about 40 minutes and then dissolved in 5 µl of a DNA loading solution (83% deionized formamide, 8.3 mM EDTA, and 1.6 mg/ml Blue Dextran). The samples were then heated to 90C for three minutes and loaded into the gel sample wells for sequence analysis using the ABI377 sequencer. Sequence analysis was performed by importing

ABI377 files into the Sequencer program (Gene Codes, Ann Arbor, MI). Generally, sequence reads of 700 bp were obtained. Potential sequencing errors were minimized by obtaining sequence information from both DNA strands and by re-sequencing difficult areas using primers annealing at different locations until all sequencing ambiguities were removed.

- 5 The following Table 5 contains the sequences of the polynucleotides and polypeptides of the invention. Start and stop codons within the polynucleotide sequence are identified by boldface type. The transmembrane domains within the polypeptide sequence are identified by underlining.

Table 5

The following DNA sequence nGPCR-Seq1011 <SEQ ID NO. 1> was identified in *H. sapiens*:

CAGAAATCATGACTTTGGTTTCTTTTTTCTCTTTCCTCTCCAAGCCATTGATAATGCTCC
TTAGCAATTCAAGCCTGGAGGCTATCCCAGCCTTCTTTTCTCCTGGTAGGGATTCCAGGT
TTAGAGGAAAGCCAGCACTGGATTGCACTGCCCTGGGCATCCTTTACCTCCTTGCTTTA
GTGGGCAATGTTACCAATTCTCTTCATCATCTGGATGGACCCATCCTTGCACCAATCTATG
TACCTCTTCCTGTCCATGCTAGCTGCCATCGACCTGGTTCTGGCCTCCTCCACTGCACCC
AAAGCCCTTGCACTGCTCCTGGTTCATGCCACGAGATTGGGTACATCGTCTGCCTGATC
CAGATGTTCTTCATCCATGCATTCTCCTCCATGGAGTCAGGGGTACTTGTGGCCATGGCT
CTGGATCGCTATGTAGCCATTTGTCACCCCTTGCAACATTCCACAATCCTGCATCCAGGG
GTCATAGGGCGCATCGGAATGGTGGTGGTGGTGGAGGGGATTACTACTCCTTATCCCCTTC
CCCATTTTGTGTTGGGAACACTTATCTTCTGCCAAGCCACCATCATAGGCCATGCCT

The following amino acid sequence <SEQ ID NO. 68> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 1:

QKS*LWFLFSLSSPSH**CSLAIQAWRLSQPSFLLVGIPGLEESQHWIALPLGILYLLALVGNVTILFII
WMDPSLHQSMYFLSMLAIDLVLASSTAPKALAVLLVHAHEIGYTVCLIQMFFIHFSSMESGVL
VAMALDRYVAICHPLHHSTILHPGVIGRIGMVVLVRGLLLLPFPILLGTLIFCQATIIGHA

The following DNA sequence nGPCR-Seq1012 <SEQ ID NO. 2> was identified in *H. sapiens*:

AAAAGATACTGAGAGGAAGTCAAGGACCAGAAAGAAATAACCACTAGAAAGAGCTGCACA
GTTCTAGGTATATTTGATTCTATTTTTTTCTTTAATTTCCACCAGGTGCAATCACCAGT
ACTGCCTCAATTTACTTCAGGATTTTGGAGGGCACCCACCTTCCCCCTTGTCTCCTCACA
CAATGACCCTGGGATCCCTGGGAAACAGCAGCAGCAGCGTTTCTGCTACCTTCCTGCTGA
GTGGCATCCCTGGGCTGGAGCGCATGCACATCTGGATCTCCATCCCACTGTGCTTCATGT
ATCTGGTTTCCATCCCGGGCAACTGCACAATTCTTTTTATCATTAAACAGAGCGCTCAC
TTCATGAACCTATGTATCTCTTCCTGTCCATGCTGGCTCTGATTGACCTGGGTCTCTCCC
TTTGCCTCTCCCTACAGTCCTGGGCATCTTTTGGGTTGGAGCACGAGAAATTAGCCATG
ATGCCTGCTTTGCTCAGCTCTTTTTCATTCAGTCTCTCCTTCCTCGAGTCCTCTGTGC
TACTGTCTATGGCCTTTGACCGCTTTGTGGCTATCTGCCACCCCTTGCACTATGTTTCCA
TTCTCACCAACACAGTCATTGGCAGGAT

The following amino acid sequence <SEQ ID NO. 69> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 2:

KILRGSQGPERRNH*KELHSSRYI*FYFFSLISTRNQHQCYNLLQDFGGHPPSPSPHTMTLGS LGN
SSSSVSATFLLSGIPGLERMHIWISIPLCFMYLVSIPGNCTILFIKTERS LHEP MYLFLSMLALIDLGLS
LCTLPTVLGIFWVGAREISHDACFAQLFFIHCFSFLESSVLLSMAFDRFVAICHPLHYVSILTNTVIGR

The following DNA sequence nGPCR-Seq1013 <SEQ ID NO. 3> was identified in *H. sapiens*:

GCCATTAGCACCAAGTGTTGCCTGTCCATCCTGTGGCCTACCATCTGGTATTACTGCAGC
 CATGCAGGATCCCTGTCAATGATCATGTGTGCTCTTCTCTGGGCCCTATCCCTGCTGCTG
 AAACCTCCTGGAGGGTTACTACTGTGCTGTATGTGTGCCACATTTTCTTTATCCAATTAAC
 TATGGATAGGCACATTGATTTTCATGTCTTTGCTATTGTGAATAGAATTGCAATGAACATA
 CAAGTGCAGGTGTCCTTTTAGTAGAACGATTTATTTTCTTTTGGATATATACCCAGTAGT
 GAGATTACTGAATCAAATAGTAGTTCTAAGTTATTTGGGAAATCTCCGAACTGCTTTCCA
 CAGTGGTTGAACTAATTTACATATCCTCCAACGACTTATAAGCATTCTCTTTTCTCTGCA
 GCCTCACCAGCATCTGTTGTTTTTTGCTGGAGGGCAGCAGCATGATCTCGGCTCACTGCA
 ATCTCCGCCTCCCAAGTTCAAGCGATTCTCTACCTCAGCTTCCTGAGTAGCTAGGATTAC
 AGGCACCCGCCACCATGCCCGGCTAATTTTGTATTTTGTAGTAGAGACGGGGTTTCATCA
 TCTTGGCCAGGCTGGTCTTGAAGCTCCTGATCTCATAATCCACCCACCTCGACCTCCCAA
 GTGTTGGGATTACAGGCGTGAGCT

The following amino acid sequence <SEQ ID NO. 70> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 3:

AISTKCCLSLWPTTIWYYCSHAGSLSMIMCALLWALSLLLKLLEGYYCAVCVPHFLYPINYG*AH*F
 HVFAIVNRIAMNIQVQVSF**NDLFSFGYIPSEITESNSSSKLFGKSPNCFPQWLN*FTYPPTYKHS
 LFSAASPASVFCWRAAA*SRLTAISASQVQAILYLSFLSS*DYRHPPPCPANFCIFSRDGVSSSWPG
 WS*TPDLIIHPPRPPKVLGLQA*A

The following DNA sequence nGPCR-Seq1014 <SEQ ID NO. 4> was identified in *H. sapiens*:

GGAACCCAGCCAGCTCCGCCCTCTCCGGTCAGGAGACTCTTCATCCATTTAGCAGCCGC
 CGACTTACTAGTCACTTTTGTGGTTATGCCCTAGATGCCACCTGGAATATCACTGTTCA
 ATGGCTGGCTGTGGACATCGCATGTCCGACACTGATGTTCTGAACTAATGGCCACGTA
 TTCTGCAGCTTTCCTGCCTGTGGTCATTGGATTGGACCGCCAGGCAGCACTCAACCC
 GCTTGGATCCCGTTCAGGTGTAAGGAACTTCTGGGGGCGAGCCTGGGGACTTAGTTTCCT
 GCTTGCCTTCCCCCAGGTGAGTGACCTAGGACTCAGGACCGGGCAGGACAGGGATTGGG
 TCCATAGCATGAGTTAAAGGGTGCGCTTGGGGGCCATTAGCCATTAATTCTCAGGGAGTA
 AGCCTCTGCTTGCTTTTTTTTTTTTGGCCGGCTCACTGCAACCTCCGCCTCCCGGGTTC
 AAGCAATTCTCCTCCCTCAGCCTCCCGAGAAGCTACAGGCGCCCGCTACCATGCCCGGCT
 AATTTTGTATTTTGTAGTAGAGGCGAGGTTTCACCATGTTGGCCAGGTGGTCTCCATCTC
 TTGACCTCATGATCCACCTGTCTCAGCCTCCCAAAGTGCTGAGATACAGGCGTGAGCCACC

The following amino acid sequence <SEQ ID NO. 71> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 4:

EPSQLRPSVRRLEFIHLAAADLLVTFVVMPLDATWNITVQWLAVDIACRTLMFLKLMATYSAAFL
 PVVIGLDRQAAVLNPLGSRSGVRKLLGAAWGLSFLAFPQVSDLGLRTGQDRDLGP*HELGALG
 GH*PLILRE*ASACFFFLPAHCNLRPLPGSSNSPPSASREATGARYHARLIFVFLVEARFHHVGQVVS
 IS*PHDPPVSASQSAEIQ*AT

The following DNA sequence nGPCR-Seq1015 <SEQ ID NO. 5> was identified in *H. sapiens*:

CAAGGCTCATGCCTCTGCACTCTAGCCTGGACAACAGAGTGAGACCCATCTCTAAACACA
 TAAAAATAAAAAAAGAGTACATGGGAATATTGCATAGGTTATAATATAAATGCTGTAC
 CATTTTATATAAGGGACTTGAGCATGCATGGATATCAGGGGCCGGGGGGGTGGTGTCTG
 GGACTAATCCCCAAGGATACTGAGGGACAACAACTATGGACCCCAAACCAGGTGCTCT
 GTGAATGAAGAGCTTTCCTCTGAGATGAGGGAAGCAGGGAGAAGATGGAACTGGGGAAG
 GCTTTGTGGGAGAGGTGGCAAATGAGCAGGAGCTAGAACAGAATTCAAATGGGGGTTTGG
 GGAGGAAAGGAGGAAGACACAGCTCAAAAAGAGAAGTCTACAGCCATACCCCGCTGAATG
 CACCTGATCCTGGCTGATCTCAGAAGCTAAGCAGGGTTGGGCC

The following amino acid sequence <SEQ ID NO. 72> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 5:

QGSCLCTLAWTTE*DPSLNT*K*KKRVHGNIA*VII*MLYHFI*GT*ACMDIRGRGGGV LGLIPQGY*
 GTTNYGPQTRCSVNEELSSEMREAGRRWKL GKALWERWQMSRS*NRIQMGVWGGKEEDTAQKE
 KSTAIPR*MHLILADLRS*AGLG

The following DNA sequence nGPCR-Seq1016 <SEQ ID NO. 6> was identified in *H. sapiens*:

CTGGAAAGGGGGGAAATCACTCGTGCCTGCTGCGCTTCCCCGCCGGCGGCCCCAAATGGC
 AGGTGCTCTACCACTGCAGAAGATCGCAGTAGCCTTCGTGCTGCCGCTGGCCACGCTGG
 GCACCTGTTCGCTGCTGCTGCGCTTCCTGCGACTGTGGTGCGCACGCTGGCCGTCGAGGG
 TCAGGCGCCGACTGCGTTCCCGAGTCACCTGTGCGCTGGCCTGCGTGCTACTGGCCTTCG
 TGCTCTGCTGGCTGCCAGCCAAGCGTTCACTCTGAGGGGTGCTGATCAAACCTGAACG
 CCATGCCCTTGGACCGCGCTTACTTCCTGGCTCAGGCCTACCTCTTCCCGGTCTCCATCT
 GCCTGACGCACTGCAACAACAGCCTCAATCCGCTGCTTTACTGCCTGCTGCGGCGCCACT
 TCCGACAGGGCCTTCGAGAGCTGTGTAGCTGAGCCCAGCGGCCGGTGCCCCCTCCGAGCAA
 GCTCCACAGGCAGCGCCCCAGCGGCTGCACTCTTCCAATGAGGGCCCGCTTGTCGCTGCG
 TCAGTACCAAGGGCATGGGGTAAAAGTGGCTCATATC

The following amino acid sequence <SEQ ID NO. 73> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 6:

GKGGNHSCLLRFPAGGPKWQVLYHLQKIAVAFVLPLATLGTCSLLRFLRLWCARWPSRVRRRL
 RSRVTCALACVLLAFVLCWLPSQAFTL*GVLIKLNAMPLDRAYFLAQAYLFPVSICLTHCNNSLNP
 LLYCLRRHFRQGLRELCS*AQRPVPLRASSHGSAPAAALFQ*GPACRCVSTKGMG*KWLI

The following DNA sequence nGPCR-Seq1017 <SEQ ID NO. 7> was identified in *H. sapiens*:

ATCCTTCTCCTACCCATCGTTTCAGACTCATGTCCTTTATCAGTCATCTTGATTCTTTTC
 TCTGTTGCTTTCCCTCATCAGGTAGCCGATGTTGATTGTGCTGGATTCTTGATTGCCTG
 GATTCTTATGCAGTGGTGTCTGTGTGGTCAGCTTTTGAAGGCCAGACTCCATTCCCAT
 ACAGCTCTCTGTGGTGCCAACCTACTTGCAAAATCTGCAGCGATGTACAATCCCATCAT
 TTACCAAGTTATTGATTACAAATTTGCCTGTTGCCAAACTGGTGGTTTGAAAGCAACCAA
 GAAGAAGTCTCTGGAAGGCTTCAGGTAAACTTCAGAAGCTGGAAATGAATTACACTCTC
 TTTGTTTCAAAATCCGGCAGGGTTCAAGGTACTCAGATGTGCTGTCTTCTTAGGGTTAA
 GCTCATCGCCTAGGAGTAGTGTAGGAAGGACTTTATTTTCTGTTTATCAAAATTCCTGAA
 ATCAAGTAATCAGCTATGTAGAGGTTGTATGACATGGATAGATAGTGAGAAGTGATTC

The following amino acid sequence <SEQ ID NO. 74> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 7:

SFSYPSFQTHVLYQSS*FFSLLLSLIR*PMLICAGFLIAWIPYAVVSVWSAFGRPD SIPIQLSVVPTLLA
 KSAAMYNPIYQVIDYKFACCQTGGLKATKKKSLEGFR*NFRSWK*ITLSLFQNPAGFKVLRCAVF
 LGLKLIA*E*CRKDFIFCLSKFLKSSNQLCRGCMTWIDSEK*F

The following DNA sequence nGPCR-Seq1018 <SEQ ID NO. 8> was identified in *H. sapiens*:

AGGCTGAGTGATCTATGATTGTACCATTGCACTCCAGCCTGGGTGACAGAATGTGACCCT
 GTCTCAAAAAGAATAATAATAATCATTCCATAAAAAGTATCAAATGGAGAAATAAAT
 CATCAGTGGGGTCTCGGAGGGGACCAGGGGCTGCAGTGACAGGCAACCTGGGGCCCTGAC
 ACAGGGTCATTCTGTTCAGGAAGATGAATGCTTCCAGATGCCTGTCTGAGGAAGTGGG
 GTCCCTCCGCCCTCTAACCATGGCTGTCTGTCTGCCTCCTTTGTCGTCGGAGTGCTGGG
 CAATGGGCTGGTGCCGTGGGTGACTGTCTTCCGCATGGCCCGCACAGTCTCCACCGTCTG
 CTTCTTCCACCTGGCCCTTGCCGATTTTCATGCTCTCACTGTCTCTGCCCATCCTCGTGTA
 CTATATTGTCTCCAGGCAGTGGCTCCTTGGAGAGTGGGCCTGCAAACTCTACACCGGTTT
 TGTGTTCTCACCTTCTCCACAGTAACTGCCTCCTGGTCTCATCTCTGTGGACCGTTG
 CATCTCTGTCTCTACCCCGTCTGGGCCCTGAACCACCGCACTGA

The following amino acid sequence <SEQ ID NO. 75> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 8:

G*VIYDCTIALQPG*QNVTL SQKE***SFHKKYQMEK*IISGVSEGTRGCSDRQPGALTQGHSCSRK
MNASRCLSEEVGSLRPLTMAVLSASFVVGVLGNGLVPWVTVFRMARTVSTVCFHLALADFMLS
LSLPILVYYTVSRQWLLGEWACKLYTG FVFLTFSTSNCLLV LISVDRCISVLYPVWALNHRT

The following DNA sequence nGPCR-Seq1019 <SEQ ID NO. 9> was identified in *H. sapiens*:

TATTTGGTGTGTTGGCTAGCCAGTGCTTCTCAGAATGGGAAATGGTAAACAAGCAGTCT
CCATGATGACCCCCGTCATACCTATGCTTCCAGTATATGACACTTGAGGAGAAAGAAGCA
CCTCTGAAGGCTGATGCATGTCAGGAAGCAAATGCTGGTATATATGTTGAGATACTTCAG
GTAGAAGCACACTAGGTCAAGGGGCCCCCTGGAAAGGCCAGTGGTGGCTGATGTAATAGTA
AATCCAGAGGGGTAAGGACAACATGTGTGCAAGGTCAGCCACAGAGAGGTTGATAATGAA
AATGATGACTTTATTTTTCTTGTTGATGAAGTGACACAGAACCCACACGGCCACAGTGTT
GGCTAGAAGACCAGGTATGAATATGAGGATATAGGTAGTTTTATAGAGGGAGTACTGAAA
TGGCATTGTAAGATCAGTGCATTTTGCTCTTGCTGTTTGTGCTGTTATTCCCATCTTG
AAGACTTATGTTCTTCCCTAGTAAAGCATTAAATGACAATTCGGCAGAAAATAGAGT
AAAATTAGAGTCAAGGGCATGTCAGTTCATGTTTGGGTATACAAATATATTTGTTTTCTAAT

The following amino acid sequence <SEQ ID NO. 76> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 9:

*KTNIFVYPNMN*HALDSNFTLFSAEIVILMLY*GRNISLQDGNNSTNSTRAKCTDLQMPFQYSLYK
TTYILIFIPGLLANTVAVWVLCHFINKKNKVIIFINLSVADLAHMLSLPLWIYYIISHHWPFQGPLD
LVCFYLKYLNIYTSICFLTCLSLQRCFLLKCHILEA*V*RGSSWRLLVYHFPP*EALASQQHQI

The following DNA sequence nGPCR-Seq1020 <SEQ ID NO. 10> was identified in *H. sapiens*:

TTTCAAATATTTGAAGAGAGGTACCATGCTCCACCTTGGTCTCTTTTTTAGGTCTAATA
CCCTGAGCACCTCAAATCCTTTTAAATTATATTACTCCAGGCCTTCACCATCTAGGTT
AACTTCCTTCAGTTTTATTAAAAAGTATTCATAAACTGACACTGTGAATCAGAAATGGG
TAATTTTATTTATTTTGAGCATAACTACTACTAAAAGAAATTTACAAAAAACGTTATTTG
TAAGCTTCCATACCCAAGAATCAGAATGTGATTTTGTCCAAATAATAATTTAGCCTGCTG
AGAAAAATGCCTGCCCCCGATCTCGTACCTGGTGATCCAAGATGGGAAAGATATTAAATC
AGAAATCATCTGCACCATCCTGATACTGACTTTTATACTCCATTGGGTGCTTTTTAGATT
GTATTTTACTACCTATGTCAAAGACCGATACTGGTCAAGACTTATTACCCACCAATGGGC
TGTAAGAGAGACTGCTGAAA

The following amino acid sequence <SEQ ID NO. 77> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 10:

FSSLFTHAWWVISLDQYRSLT*VVKYNLKSTQWSIKVSIRMVQMISDLISFPSWITRYEIGGRHFSQ
QAKLLFGQNHILILGYGSLQITFFVNFF***LCSK*IKLPISDSQCQFMNTF*IKLKEVNLDGEGGLGVI*
FKRI*GCSGY*T*KRDQGGSMVPLFKYLK

The following DNA sequence nGPCR-Seq1021 <SEQ ID NO. 11> was identified in *H. sapiens*:

TAGTGGCTGGCATAGAATAAGTGGTGAAAAGTGTGGTTAAGAATATGGATAAGAAAACAA
GAAGAGGAGGAAGAGGAGCAAGAGCACATGGGGGAGGAGGAGGAATATCACCAACAGAGA
ATGGCACATCCTAAAGCAGGGACATGAAAGCTGTCTGCAGTCATCATAAGAAAGGAAGTG
GTGATAATTTAAGCAGTTTATGTAGTTTGAAAGTTTGAGCCTAAATATACCTTGGCTATT
TTAGGTAGCATGGAGAATGTGTCTGCATTGTCACTGTTGACTGTGGAGAGTCCCACGTC
CATGTTTGACTATTGTGATGACTCTTTGGAGAGGGTCAAGTCTGCTCTTGACATCTTTTC
CATGATCATCTACACAGTGACTTTCTTCCCTAGGCTTGGCTGGCAATGGCCTTGTCATTTG

GGTAGTTGGATTCCACATGTCCTGCACAGTCAACACGGGTGTGGGTGGTACCTCAACCTGC
CCGTGGCTGACTTCATCATCATCTTCCCACTGCTTCTCCAGCTGGTTATGGTAGCTCTGT
AACCCCTTTGGCCAGCTGCTCTGTAAACTCAATAGCACCATGTCTATTTTAACTTTCTGG
CCAGTGTCTTCCTTCTGACCCTCATCTTCATGGACCACTGAC

The following amino acid sequence <SEQ ID NO. 78> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 11:

VAGIE*VVKTVVKNMDKKTRRGGRGARAHGGGGGISPTENGTS*SRDMKAVCSHHKKGSGDNLS
SLCSLKV*A*IYLGYP*VAWRMCLHCHC*LWRVPRPCLTIVMTLWRGSSLLTSFP*SSTQ*LSS*A
WLAMALSFG*LDSTCPAQSTRCGWYLNLPVADFIHFPPLLQLVMVAL*PFGQLLCKLNSTMSIFNF
LASVFLLTIFMDH

The following amino acid sequence <SEQ ID NO. 135> is another predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 11:

SGWHRISGENCG*EYG*ENKKRRKRKSTWGRRRNTNREWHILKQGHESCLQSS*ERKW**FKQF
M*FESLSLNIPWLFLGSMENVSALSLLTVESPTSMFDYCDDSLERVKSALDIFSMIYTVTFGLGLAG
NGLVTWVVGFMSCVTNTVWVVPQARG*LHHHLPTASPAGYGSSVTLWPAAL*TQ*HHVYF*LS
GQCLPSDPLHGPL

The following DNA sequence nGPCR-Seq1022 <SEQ ID NO. 12> was identified in *H. sapiens*:

ACTTTATTTCTTTTGTGTTGCGTGGGAAACATGATGGAAGCTTACACACTATAACAAGAAAA
TGGTACTTTTTTAAAGCATTATAACCAAACACCAGACATTACTATAAAATATGTATTAAA
AGAAATCTACTTTGACATAGGTTAAAATCCTTAAACATGTCAGAACAGATGATAGGCTA
TAAATAGAAATATTCTTGATCTCTGAGGTTATTCATAATCTTTGTTTATTACCTGCATAA
AATATGTACAGTTCTAACACTCAATCCACCTAGCTTTAACTGTCAGGGAATGAGAAACCT
GCCAACTTACCATAAGATAAATAGCAGATTTTCAAATATCGATCCAGGCTGACAGCAGTC
ATGGTGATAAGGCTTCCACAGCCAAAGAAAAATCCAGCCCATCCATACCAGCGGCAGCCG
ATCCAGCCAAACACCCAGCGGTGACAAAAGCAAGAGATGATGGTGAACGGCTTGCCTACA
ACTAGAGCACCAAGTGACTTGTCAACAGACGTTCTCTGGTTACTATTTCCCCACCTACC
TCAACTCACCTGAACCTCCTCCCTAAAGCACGGGGACACATGTGAACGCACACACACAC
CCTTGATTACACAGATTTCTAGATTAATAAAAGCCCAGCAGTTATCTATGAATAAACTC
AGTTTGAAGCTACCCAGAGAGGACTTTCAGTCA

The following amino acid sequence <SEQ ID NO. 79> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 12:

D*KSSLGSFKLSLFDNCWAFINLGNLCNQGCVCFTCPVL*GRRFR*VEVGGEIVTRGTSVDKSL
GALVVGKPFTHISCFCHRWVFGWIGCRWYGWAGFFFGCSLITMTAVSLDRYLKICYLSYGLAG
FSFPDS*S*VD*VLELYIFYAGNKQRL*ITSEIKNISIYSLSSCSDMFKDFNLCQSRFLIHIL**CLVFG
YNALKKYHFLV*CVSFHHVSHANKRNK

The following DNA sequence nGPCR-Seq1023 <SEQ ID NO. 13> was identified in *H. sapiens*:

ACAATAGGTTTGATACTTTAATCACCAGGCATTCAATAGGGATCCTAATATTTCCCATCTT
CTGTAGTAGTAGTAGAAGCGAGGACACTAAGGTGTCTCACTTGCCACCTTGTGAGAACAT
ACAGAGGACCCTTGAACAGATCTCTTTGGTCTTGGCTCCATAGACAAGGGGGTTGACTAC
AGGTGGTAGCAGCAAGTAGGTATTAGCCATAACCATATGGAGGAGGGAGGTGGGACCACC
CAGCCTATGCACCACCGAGAGCCCAATGAGGGGTACATAGAAGACCAGAACAGCACAGAG
GTGGGAGATGCAGGTGTTGAAAGCCTTGAGTGCTGCCCTCCGAGAGGACAGCTCCAAAAC
AGCCACAGGATGAGGATATATGAGAAGCCAATGAAGAGAGAGTCCACACCCATGACTGA
GAGGATGATGAAGAGTCCATAAACCACATTGACCCTGGTGTGTCAGTACAGGACAGCTTCAT
AATATCTTGGTGCAGACAGAAGGAGTGTGTGACAGTATGTGTTTGGCAGTAGGA

The following amino acid sequence <SEQ ID NO. 80> is the predicted amino acid sequence derived from

the DNA sequence of SEQ ID NO. 13:

SYCQTHTVTHSFCLHQDIMKLSCTDTRVNVVYGLFIILSVMGVDSLFIGFSYILILWAVLELSSRA
ALKAFNTCISHLCAVLVIFYVPLIGLSVVHRLGGPTSLLHVVMANTYLLPPVNVNPLVYGAKTKEIC
SRVLCMFSSQGGK*DTLVSSLLLLLQKMGI LGSLLNAW*LKYQTYC

The following DNA sequence nGPCR-Seq1024 <SEQ ID NO. 14> was identified in *H. sapiens*:

CTCCCTGGGCAACGGATCAGAGAACA TAGCCCGGCCCGGAGTCCCCGCAGCCTGCATGG
CCTGGACGGGGTGGCGGGGGGCCGTCCGGGCGCCGGCGCTGCGGGCTCTGATTGCGGGCGC
CTACTGGGCCCTGTGCGCTGTAGGCCTGGTGGGCAACGGCTGGTGCTAGTCCGGGTGAGG
TCCCAGCAGTGGCGCCGCCACTGGCTGCTCAATTGCTTCCTCCTCAATCTGGCAGCCACT
GACCTGCAGTTTGTGCTAACGCTGCCCTTTTGGGCCGTGGACACGGTGCGCGACTTTAGC
TGGCCCTTCGGGGGTGCCATCTGCAAGGTGATGCTGACGCTACCGTGCTCAACATGTAT
GCCAGCATCTTCCTCCTCAGTGCCATGAGCGTGGCACGCTATTGCATTGTGACTGGCGCG
CTGCCTCCGAGCCATCGGGGCGCATCACGGGCCAGCTGTGTGTGCTGCCTGCTCTGGGCT
ACGGCCGTCTGGCTACGGCGCCCAACGCCCTGTTGCGCACGGCAGCTAGGGTGGGGGGA
AAGCACTCGTGCTGCTGCGCTTCCCCGCCGGCGGCCCAATGGCAGGTGCTCTACCAC
CTGCAGAAGATCACAGTAGCCTTCGTGCTGCCGCTAGCCACGCTGGGCACCTGTTGCTG
CTGCTGCG

The following amino acid sequence <SEQ ID NO. 81> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 14:

LPGQRIREH*PGPESPQPAWPGRGGGGRPGAGAAGSDCGRLLGPVRCRPGGQRLVLRVRSQQW
RRHWLLNCFLLNLAATDLQFVLTLPFWAVDTRDFSWPFGGAICKVMLTLTVLNMYASIFLLSA
MSVARYCIVTGALPPSHRGASRASCVCCLLWATAVLATAPTALFATAARVGGKHSCLLRFPAGGP
KWQVLYHLQKITVAFVLPLATLGTCSLL

The following DNA sequence nGPCR-Seq1025 <SEQ ID NO. 15> was identified in *H. sapiens*:

TTGACTTGCGCAATGCTAGTTCATGGAGATGTCCCAGAAAATCAGTTGAAGTGGACTGTGT
TTGTTGAGCATTAAATTAATGATAGCCTGTTTATTCTTTGTGCCATCTCTTTAGTGTGTTA
CATATGCAAAATTACAAAAATGTCATCAGCTAATGTCTACCTCGAATCAAAGGGTATGTCT
CTGTGCCAGACTGTCGTCGTGGGCTCTGTAGTCATTCTTCTGTACTCTTCCAGAGCTTGTT
ATAATTTGGTGGTGGTCACCATATCTCAGGATACATTAGAAAGTCCATTTAATTATGGCTG
GGATAATCTTTTCAAGATAAGGCTCATGTAGAAGACATAAGTGGAGAAGAGTATATAGTATTT
GGAATGGTCCTCTTTCTGTGGGAACATGTGCCAGCATGGTCGGTGGTACTGTTTTTCCGGG
CACAGAGATTAAACCAGAATTTGGCACCTGCTGGCATGATAAATAGTCACAGTTATAGTTC
CAGAGCTTACTTTTTTCGACAATCCAAGACGATATGATAGTGATGACCTGCCAAGACTG
GGAAGTTCAAGAGAAGGAAGTTTACCAAATTCGCAAAGTTTGGGCTGGTATGGCACCATGA
CTGGGTGTGGCAGCAGCAGTTACACAGTCACTCCCCACCTGAATGGACCTATGACAGATAC
TGCTCCTTTGCTCTTTACTTGTAGTAATTTAGATTTGAACAATCATCATAGCTTATATGTG
ACACCACAAAATGACAGCATACCAAGTCATGATTCTTGAGTTGTTTTTCATAAATGTGT
ATATTCAATGTGTTTAAATTCCATCTACATAAACATTCCATTATCTGTTGCAACTGAAAC
AAAATCTGGAAGTGTGGCTGTGTTTGGTAAATAACACAGCTATTATTTTTGACCTCTTCAT
AGTAAATGAAGTAAATGGAAAGTTTGGAGTAGGAGAAAAGAGAGATTAGATCTTAAGGC
ACTTGATGGCCTCCAAAAATCCTGACTTTGGAACATCAAATGCATATGTGCACTTTTATCT
TTGTTCTGAGTCACTGCAGTCCCCAAAGTCATATGCCAATGTTTCACTGAAATACTGTAT
TGTACACCAAATGGAAGGCAATTTTCCTATGAAAATCAAAGCCGGTATATTCATTGGTAT
GCTCTATACAGATATCTTAATAAAAAATTTTATAGTGTGAACAGTGCACAGAGTTAAGGCAT
AAAAATGTATCATTCTTTATAAAAAATCTACTGAAAATGTGTAATCATTGAAGACAGTTCTT
TTAAGCATGATTTTAAATAGCAACTGAAATTCAATCATTTTAAACAAATGATGGTAGTAA
TCCATTAGTTATGGCCAGCAGTGTCTTTGGAGAGCCACAATAATTCAAGAGGAAAATAT
ACCAGTGAAAATTTGTGTGGCTATTTTGTAGTAGAATTGGTCAGTTGATTATTTTGTGTAATT
GAGATATATGTAGTAGTTTAAGCATGATTCTTGAAGAAAGCAATAGTGACTTTTGCATAGG
GAGATTTTGGTAGAACTTCTTGGGACTAAACAAGTTTAGAGATGCATTTAAGAATTATTC

ACAAAATGTGTAATTCTAAATTA AAAACATAAATATATTTTCAAAAGCATTGATTCTCTG
AAGCATGATATAGCTGGTCTTACCTAGTGAATCAGGATTGTCCTCAGGTAAATGAAATCAT
GATACATTATTGCAGTGAACCTCAAGTGCAATACTTTGTAAGACATATAATTCCTATGATTT
TCACATTTTATATCTTATATATGGGAAAAGCCAAATTAAATTGAATTCAGATTAATTCCA
GCATTAGACTAAATGAGCAAACCTTAAGTAAATGTACAACTAGGTAAGTATAAAACACAG
GTTAACAATATTGGAGTACTTTTAGAATTACATTAAAACTGTCTTAAATGTCCTATCCCAA
ATCTAAAAAAAAAAAAAAAAA

The following amino acid sequence <SEQ ID NO. 82> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 15:

LTCAMLVHGDVPENQLKWTVFVRALINDSLFILCAISLVCYICKITKMSSANVYLESKGMSLCQTV
VVGSVVILLYSSRACYNLVVVTISQDTLESPFNYGWDNLSDKAHVEDISGEEYTVFGMVFLWEH
VPAWSVVLFFRAQRLNQNLAPAGMINSHSYSSRAYFFDNPRRYDSDDDLPRLGSSREGSLPNSQSL
GWYGTMTGCGSSSYTVTPHLNGPMTDTAPLLFTCSNLDLNNHHSLYVTPQN

The following DNA sequence nGPCR-Seq1026 <SEQ ID NO. 16> was identified in *H. sapiens*:

CATCCATTTCTCTAGTATTTGTCACCACGGTGTGTTCTCCGCCTGTATTACAGGCCTGA
GCATGCTGAGCACCATCAGCACCAGCACCCTGTCCGTCTGTGGCCCATCTGGTACT
GCTGCCACTGCCCCACACACCTGTCAGCGGTGTCATGTGTGTCCTGCTCTGGGCCCTGTCCC
TGTTGCAGAGCATCCTGGAGTGGATGTTCTGTAGCTTCTGTTTAGTGATGTTGACTCTG
ATAATTGGTGTCAAATATTAGATTTCTCACTGCTGTGTGGCTGATTTTTTTAATCTGTG
GTTCTCTGTGGGTTCAACCTGGTCTGCTTGTGTCAGGATCATATGTGGATCCCAGAAGATG
CCGCTGACCAGGCTGTATGTGACCATCCTGCTCACAGGGCTGGTCTTCTCTTCTGCAGC
CTGCCCCCTCAGCATTCAAGTATTCCTATTATACTGGATCGAGAAGGATTTGGATGACTTA
CCTTGTGTTGTTGTTAATTTCATTTTCTGTCTGCTCTTAACAGCAGTGCCAACCCC
ATCATTACTTCTTCATGGGCTCCTTTAGGCAGCTTCAAAACAGGAAGACCCTCAAGCTG
GTTCTCCAGAGGGCTCTGCAGGACATGCTTGAAGTGGAT

The following amino acid sequence <SEQ ID NO. 83> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 16:

SISLVFVTTVLFSACITGLSMLSTISTEHRLSVLWPIWYCCHCPHLSAVMCVLLWALSLLQSILEW
MFCSFLSDVSDSNWCQILDFLTA VWLIFLIXSVVLCGFTLVLLVRIICGSQKMPLTRLVVTILLT
GLVFLFCSLPLSIQXFLLYWIEKDLDDLPCVVRLISIFLSALNSSANPIIYFFMGSFRQLQNRKTLKLV
LQRALQDMLEVD

The following DNA sequence nGPCR-Seq1027 <SEQ ID NO. 17> was identified in *H. sapiens*:

AGGCGGAGGTTGTGGTGAGCCGAGATGCGCCCCGCACTCCAGTCTGGTGACAGAGGGGAGA
CTCCATCTCAAAAAAAAAAAAAAAAAACGCTGGGGTTACAGGCGTGAGCCACCTTGCCCAG
CTTGATTATATCTTAAATATGAAAATTAAATAATAGAAAAAACTTTTTTGATGGTACCT
ATAGAGATATTATTAATCTTTTCATAGGTTTAATTAATCAGAGCTGCCTATTTTTCAACA
GTGCTTTCAGCAACCATTTTAAAGCATCAGGTGACAAAATATGTTGAATGGGTCATGATC
CTTACTGTAATGTAAATTTACGTGAATTTCCACCTCAGAAGATGATGTGCCATATTTTGC
ATAAGATGTTTTGATATAGGGGAGACTTAACATTTCAATTGTCAGAAACCAAAAAAATTTT
AGAGGCTTTCTAAAATAGGGAAATATTTTACAGAACACACAAGACTCATGGACTAAAACG
GAATTAGGTATTAATTCTCTATTTAACATAAAGTCTCCCC

The following amino acid sequence <SEQ ID NO. 84> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 17:

GDFMLNRELIPNSVLVHESCVFCKIFPYFRKPLKFFWFLTMKC*VSPISKHLMQNMAHLLRWKFT
*IYITVRIMTHSTYFVT*CFKMVAESTVEK*AALIN*TYEKINNISIGTIKKVFSIILIFIKI*SSWARWL
TPVTPAFFFFFLRWSLPLSPDWSAGRISAHNLR

The following DNA sequence nGPCR-Seq1028 <SEQ ID NO. 18> was identified in *H. sapiens*:

AAAACATCTGGCTTTTAAAGGTTACTTTTCATGTACATAGTTTAACTTCTAATGAACAA
TTGAGCTTTAGTAACTAACCTGTTATTTTCAGTTATCTTAAAAGGAAAATAAAGGTTGGAG
TTTTTGTTTTACATATAAATTATTCACATCTCACCAGGCTTCCAACATTTCTAGATTG
GTACTGAAAACCTTCAATTTTGTAAAGATTATTGTACCAGATGTATTACTATTAAAGTACA
GAAAATTAAACAAAAGGTATATGCTACACATATATAAAAGAAGACTTCATTCACTAAAGA
CAAAGTGATAGTTTGCTTGATTAAATCAAAGTCAAGCCTATATAAGTATGAAAATATTAA
CAATGTCAAATTAGATACATATTAAGGCTTTATTCCTAAAAAAGTAAAGTGATAATATT
CAGAAATTTTAAAGCTTTTCTTTTCTTTTACACTTTTATATCTTAAGTCATAGAGCATGT
TAAAGGAAATCTACCTTGACAGTGTGATGGACAAGATG

The following amino acid sequence <SEQ ID NO. 85> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 18:

KTSGFLRLLFMYIVLTSNEQLSFSN*PVISVILKKG*RLEFLFLHINYSHLTRLPFLDLVLKTSILLRL
LYQMYYY*STEN*TKGICYTYIKEDFIH*RQTDSLDLIKVKPI*V*KY*QCQIRYLRLYSLKK*SDN
IQKF*AFLFLHFYILSHRAC*RKSTLTV*WTR

The following DNA sequence nGPCR-Seq1029 <SEQ ID NO. 19> was identified in *H. sapiens*:

TTTTTCTTCTGCATCATGATCCCAGTGTAATGGCATTCTTCTATTTTTTAAACATATA
TATCAATATATTCTTTGTTTATACTTGCTATTACTATTCCAACATTTTTTGGGGGACTGG
GGGCAGAGATCAACCCTGAGACACTGAGAAAGCTGCATGAAGCCAGGAAGTATGTTTGTC
TTTTTCACTGTTATACCCCCAACCCCTGAAAACAGTGCATGACATATAATAGAGGCTTAAT
AAATATTTGTGGAAACAAAACAATGAATGAGTCTTTATCTAAGGAGACTTAGCTACCATG
ATTAAGTTCAGTAAGGTAATTGTGCTCAAAGGAAGTCCCATGGCAATGATCACATTAAGA
ATGAAAATCCACATGGAATATATGATGCTCAAATTGCAAGAGCTACCTGATTTTAAGCAC
CTGTTATGTGCCAAGCCCAGTGCTAGGTGTTTCAATCCTCACAACGCTTCAAAATAGAAG
TGACTTTTCCCATTTTGAAGATGAGAAAAGTGAAGGCTGAGGCTCAGCTACTAATAAG
TAGCTGTGGAGGAAGTGGATCCCTTAGCCAATGCACTCCAAAATCTATGCCTTTGCCATC
ATACTGTGCCTTCTCCCAGATTTCTGTATGGATTACTGATGTTTTTTTCAAGCAAATACA
CAATCAAATTAAATGAGGACATAAGAACTCAAACATTGCTCCAGCAATGAGTACAATAAA
CAGTGTCACATATGTATATATGCATATA

The following amino acid sequence <SEQ ID NO. 86> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 19:

GLKHLALGLAHNRCLKSGSSCNLSIYSMWIFILNVILAMGLPLSTITLLKLIMVAKSPXIKTHSLFCF
HKYLLSLYYMSCTVFRVGGITVKKTNIVPGFMQLSQCLRVDLCPQSPKNSWNSNSKYKQRIY

The following DNA sequence nGPCR-Seq1030 <SEQ ID NO. 20> was identified in *H. sapiens*:

TACAGCTGCCTTGGTACAGTACACATTTGTTTTGTTTAAATGGACAATTTTGGGGGGCCTTG
AGCTTTGAATATGGGTTATGGTTTTTTTAAATCTGGAGCAAGATCTCAGATTACAGAGTGAA
TAACACATGGGATTCAAATGGCTGTATTTCAGAGATAAAGCAGAGGGGCCAGAAAAGCATCA
ATCCCCCAGGACCAAGCGTAGGCCAGGAGGTCTGGATATGTGGACAGAGGAACAGAGCAG
AAAGGGTCACAACAAAGGAGGAGAGAATCACCAAGGCTCTCTTCAGCCTGACTGTAGCAC
TCCATAAAAGTGTCTGCAGCCTCCCCTGGGGGTGGGAGGTAATAAGGATACTGAGTCAAT
TTCAAGCAATCAGCAAATCCCTTTAAACTAGATCCAGAATTTATATACCTCCATGTTGAA
GAAGGAAGAGTCAGTATTCTCCAAGGTCTCACAGCCAGAAAGCTGTGCTACCAGGATTCA
CAGCTATGCTTCGCTTTCAGCTTCAATACTGGTCATTTTGTGTCAAAAATAATCCTGCC
TATTATTCCTCTTCTTTTTCAGAATGAATAAGAAAATTAACCATCCAATAGGCATTGAGT
GGAATCTTGGTTATAAGACTGTGAAAAATAAATATAGCTCAAGACACTGTCTGTTTTAGT
CTCAAGGCTCTTGACTTATGAAGTGGCTGGGCACTATTTATTTAAACATCAATAT

The following amino acid sequence <SEQ ID NO. 87> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 20:

IDV*INSAQPLHKSRALRLKQTVS*AIFIFHSLITKIPLNAYWMVNFLLHSEREEE**AGLVFDTK*PV
LKLKAKHSCESW*HSFLAVRPWRILTLPSSTWRYINSGSSLKGFADCLKLTQYPYYLPPPGEAADT
FMECYSQAEESLGDSELLCCDPFCVPLSTYPDLLAYAWSWGIDAFLALCFISEYSHLNPMCYSLC
NLRSCSRLKNHNPYSKLLKAPKIVH*TKQMCTVPRQL

The following DNA sequence nGPCR-Seq1031 <SEQ ID NO. 21> was identified in *H. sapiens*:

CTTTGCCAAACAATTTACAAAATATTTTTATATTTAAAGTAAACTCAGATAGTGATTATA
AATAATAAAATAAATTTAAACAAAAAATTTTCTAACTATATTTAGACCAGCACTATCTA
ATTATGTGTTTGATAAAAATAAAAATAAACATATTTTGGATCACTGATATTTTTATCAT
AATTGAATGTCTTATAAATAATTCTGCCATTAGAAAAATTGTATAATGTCCTTAATTCTC
CACAATGAGTTATATTATGTTACCACTGAAATGAACAAACACAATATACGTAAGTGGCGA
AATAGTGTGCTCACTACAATTTAAATATCATTTAATTTAACATTTATTTAAACCAACAT
ATTTGACAATATGAATTTTTAATTTATACTAAAACAAGTTTTCTTTAAATGTTCTTAAA
TGAAAATCATTTCTGCCAACAAAAAATGAAGAAAGAGAAATTTGACAATTCTAAATTTCT
ACTTTATGCAACTAAGAATGGGAGGGATATGTTTTTTCATACAATAAATGATAAATCTTG
TTTAGTTTATAAAGAATTAAGGGCACTAAAAACTGTGAGTATAAAATAAAAAATCCTACAG
CCTTAGTTGGTTGCCTTTCTTCTCACAAAATGTTTAAAGTGATCCTTGACATTTTCAAAA
CAGAGTTTGAGAAGCCATTTATATGAACTTTCTATTGGTAAATTAAGTACGTAGACTCTA
TCTTAAGTAATTTAATTATGTGTAGCACATATT

The following amino acid sequence <SEQ ID NO. 88> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 21:

FAKQFTKYFYI*SKLR**L*IHK*IKTKKFSNYI*TSTI*LCV**K*K*NIFWITDIFIIECLINNSAIR
KIV*CP*FSTMSYIMLPLK*TNITYVSGEIVLLTTI*ISFNLTFIKTNIFDNMNF*FILKQVFL*MFLEN
HFCQQKMKKEKFDNSKFLLYATKNRDMFFHTINDKSCLVYKELRALKTVSIK*KSYSLSWLPPFS
QNV*SDP*HFQNRV*EAIYMNFLLVN*LRRLYLK*F*LCVAHI

The following DNA sequence nGPCR-Seq1032 <SEQ ID NO. 22> was identified in *H. sapiens*:

AAATTTGCATTGATTATATACCTTATTCAGTATAGTGTGTACAGTAAACTGATGATTCAA
TATCTAAAAAGTGTCTGATCTAATCAGAGGTCAGAAGACCCTGTGGGCATGCCAATAAAG
AAGACCAAGATGTTTGAATATGCAATGCTTTCAATGTGATCTGTGAGCTCCTTCTGCAAA
TAGCCTTTTTTTCTGCAGCTCATGGGTGACCTTTGGGTGGTTCTCCTACCCAGTATGCC
ACCACAAAGAGAACCAGGTTCAACAGAAATGAGGATGATTCTGGACCGTGGGGGTCACCTCA
ACTCGGGAACGTGGCTGTGCTCATTGACATGGGAGAAGTCATGCTTGGGGGCCACTAAGTG
AAGCCATGAGGAAAAAACCACATCACCAGTACAAAGACTTCTCCACTGTCTTCTCTCC
AAAGGAACTCAAAGTTCTTGCTCTGAGTTACCAAAGTGGAATAGGGTGTCTCTAACTT
AATCTTGTCTTGCAAAGTAGAAGTTGCACTTCTGGCCATGAAGAATAACTAGTACCTAAC
TTGCCCTACTTCTGTCTAGAAATAGAAAAGTGGAGAGCAGACAGCAGACTATGATGGC
TC

The following amino acid sequence <SEQ ID NO. 89> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 22:

LLPCQXAQPRSRVEVTPRSRIILVNLVLFVVGILGRRTTQRSPMSCRKKGYLQKELTDH
IESIAYSNILVFFIGMPTGSSDLXLDQTLFRYXIISLLYTLXIRYIINAN

The following DNA sequence nGPCR-Seq1033 <SEQ ID NO. 23> was identified in *H. sapiens*:

TTTATTATGGCAGCTACAGGACTTCAGTTCCAGATAAAAATGGCTGGAGCAAGAGCAAGG
AACAGCAACAACAACAAAACACAGATTATGCTGGGGGCACTCAGCAGGAAGAAAGGCTCT

GCTTCCCCCAGAATAAGTTTCTGTCTCTAAAACACAAGCTCTTGAGCATTGTATTATTAG
 TGGTAAGAGGCTAGAGGCTGCAGCTTGGTTATTTATGCATGGCACTGTGTTTCTTCCTCT
 CTTCCTTCTTCCAATCTTTGTCTTCATTAGCAATGATGATAGAATTTCTGGGCAAAA
 TAATCCTTTATTTTTTAACTGGAAAATTTTGGCAAAATGTCACAATGTTCTAGTGTCTA
 AAAGCTCAACATACTGGGGCTTAGGAACCTTCCAGGGGAGAGACAATAAGACCACAGTCT
 GCACAGAGCCTTCTGTGTGGCTGTGACAGCGAGGACAAAAACAATCACATTAATGTTGTT
 CGTTAGGATGGGGCTTTTTTGCTGCTGCTTTTTTCATGGTAGTTTTTCACTATTCAGTCTA
 AATTTGTAAAGACCATTGTTTGTTCATTAAAGAGAACTGTTTATGTCTCAAAGTTAAC
 CCATCCTAGGTACTATTTGTTA

The following amino acid sequence <SEQ ID NO. 90> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 23:

VSVSKTQALEHLFISGKRLEAAAWLFMHGTVFLPLFFLLQSLSSLAMMIEFPGQNNPLFFNWKILA
 KCHNVLVSXKLNILGLRNFPGERQXDHSLHRAFCVAVTARTKTITLMLFVRMGLFCCCFMVFH
 YSVXICKDHCLFPLRETVYVSKLTHPRYYLL

The following DNA sequence nGPCR-Seq1034 <SEQ ID NO. 24> was identified in *H. sapiens*:

ATCAAATATTCAACACTATACAACCTATATTCTAATTTATGAGTTAATGTATTAGCAGGA
 AGACGTTGGTAGGAGAAAAATGATTCATTTTTTAATTCTGTGCAGTTTCATGATTCTGAG
 ATGATAAAAAATTTTTCACATTTATGAAAGTCAGGATGAATTTACTTTTATTTTCTTAAC
 ACAGTGGGAAAATATAATATAAAAAATTAAGGGGAACTTCTAAAAATCAATCTATAAATGT
 TATTTTGAAGATTAAAAATAAATATTGGACATCTTAGGAAGAGTAAGATAGAAATGAACC
 ACCTAAAGGGAGTATATGTGACAAAATGATGTAAATAATGCTGGTTTTACAATAAAATT
 TTGTAAATCTTTGAAAAATACATCACTAACTTTCTTTGAAAGTTACTTAT

The following amino acid sequence <SEQ ID NO. 91> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 24:

CIFQRFTKFKYCKTSILHHFVTYTPFRWFISILLFLRCPIFYFNLQNNIYRLIFRSPXFLYYIFPLCX

The following DNA sequence nGPCR-Seq1035 <SEQ ID NO. 25> was identified in *H. sapiens*:

CACTGGCACTTTTTGGGGTACACGGGCATTGTGCAGGGTTCACTGACACTTTTTGGGGTA
 TACTAGTATTTTTCAGTATTCAGTGGCACTTTGTGGGGTGCCCCAGCACTTTGAGGGATT
 CACTGGCACTCTGTGGGATGTACCAACACTTTGTGGGGGTTCACTGATACTTTGGAGGTT
 TGGTGGCACTCTGTGGGAGTGCAATTGGCCCTTTCTGGGGATCACTGACATTGGGGGTGCA
 CTTGCACTTTACAGGGGCTCACGGGCACCTTTTCAGGGTTCAATTGACACTTTGGGGGTGCACT
 GGCACCTCTCTGGGGTTCAATTGACACTTTGGGGGTGCGCTGGCACTTTGCATGGGCTCACTG
 GTACTTTCCAGGGTTCACTGACACTTTGGGGGTACACTGGCACTTTCTGGG

The following amino acid sequence <SEQ ID NO. 92> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 25:

HWHFLGYTGIVQGSLLFGLVYXYFSVFTGTLWGAPALXGHHWHSVGCTNTLWGFIDTLEVWWH
 SVGVHWPFLGITDIGGALALYRAHGHFSGFIDTLGCTGTLWGSLTLWGCAGTLHGSLVLSRVHXXH
 FGGTLALSG

The following DNA sequence nGPCR-Seq1036 <SEQ ID NO. 26> was identified in *H. sapiens*:

CCATTCCTTCTTTCTCAGCCCTGGCATGTTTCCCCTCTCAGCTGCCGCAGCTCTGAG
 CTGAAAGGTTTCCCAATGAGCTGCTGGGGGGTCCACCCCATTTGCCCCAGTAGCTCTCTG
 ACCTGCTCAACACTAATTAGCTCTTTCTCAATCCTACTCACCTATTCAGTATCCTTTAAG
 AATTTCTCAAGATATCTGTCATTTATTATTTTGAACATTGCAGTGACATTTAGGGAATT
 AAGGAAGGTAAATAATATGTTTTGTTTTGAAATTGTCTCCTAGAAGTTATTTCAAACAT

ACTGACCTGGAACCAATATGTTTTCTGTTTTTAATTCCTTGTTTAATATTTTTFAATTT
 AAGGGGTACAATATGATATTTTAGTATATGTATACCTTGTGAAATTATTAAATCAGACAA
 ATTAACATATCCATCATGTCACATACTTACCATTTTTTTTATTTCGATATGTTCTTAAAGAT
 CAAACTGCTCCTGACTTTAGCAAAAATTTTAACAAATTTATATGTGTATGAAATATATGT
 ATATATATTTATATAGGTATATATTATATACTACCATATTTGATACTTAATATGTACAC

The following amino acid sequence <SEQ ID NO. 93> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 26:

PAQHXLALSQSYSPIQYPLRISQDICHLLFLNIAVTFRELKRVNNMFCFXNCLLEVISNILTWNQYVF
 CFLIPCLIFFNLRGTIXYFSICIPCEIHKSDKLTYP SCHILTIFLDFMFLKIKLLLTLAKILTNYVVEIYV
 YIFIXVYII

The following DNA sequence nGPCR-Seq1037 <SEQ ID NO. 27> was identified in *H. sapiens*:

AGGAATCTGGGGATTGTGGTTCCAAAAAGTCTGGTTTCTTTTGGAACCAGACTGAAGCAT
 GAATTTGAGTTGGGGACAAGGGGATCCCCCACTCAAAAAAAAAAATCCACCTCATTAAAA
 ATTCCTTTGGCATGGCATATTGCTACAGAGTCTGATTGTAGTGCCAGTGTCCTTTCTAACA
 CCCTTCAAATAACAGTGCTGACAAATTCCTAAGCAGCCGTCAAATTACATGATCTTGACC
 TGGTTGGATAAAAAGTGATGCTAGCACAAAGGTGATTGATTGAGGATTATGACAGTCAGA
 CAGATGACACAGTGAATATTGGAAGTATTAATAGCAAGCTTATTCCTAATCTTTACACTG
 TAGGCAAAAGAAGTAACATGTCAAAAACACCACAGAATATTTTTATTATGGGAGGAGGCA
 AAACGTTCTTAAGCTTATAATGTAGTGGCACCTTATAGGTAAGACTTAAAGCCTCAAAGC
 TTTGTTTTAAAGCAACGACTGGTGTGATTCTCAGTCAATTTAAAGGATGAAAAGGGCTG
 TAAACTATTTTACGGTAGGAATAATAGCTACCACTTTTAAAGCACTATGTTACAGGGAT
 TTAAATATATTAGCTAATTTAAGCCTAATGGCAGCCTTGTCAGGTAGGTACCTTTGTCC
 CCAGTTTATATACAACCTGCAA

The following amino acid sequence <SEQ ID NO. 94> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 27:

AVVYKLGTKVPT*QGCH*A*IS*YI*NPCNIVLKKW*LLFLP*NSFTALFIL*ID*ESTPVVALKQSFEA
 LSLTYKVPLHYKLKNVLPPIIKIFCGVFDMLLLLPTV*RLGISLLLLIPFTVSSV*LS*SSINHLCASIT
 FYPTRSRSCNLTA*EFVSTVI*RVLERHWHYNQTL*QYAMPKEFLMRWIFFLSWGIPLSPTQIHAS
 VWFQKKPDFLEPQSPDS

The following DNA sequence nGPCR-Seq1038 <SEQ ID NO. 28> was identified in *H. sapiens*:

CAGCTGTCAATTATATAGTCAGGGGAATCATAGACTTTTAGTACTTGTACAAACTTTAGA
 AATGATCCTCTAACAAGCTCATTTTCATACTGATAAAATGTGTGTGCTAGGATTTTCATAC
 ATGCTGGGTTGAATGGGTAGGTGATAGGTACCTCCAATGTGGACTGTTAGGCCAAGAATG
 TTACATTATGAAGGGCATTTTAAATTAGGATGTGAAGCAAATGCTTGAAGTAGAAGCCTT
 CATATATTCTAGTACCCAAAGATACTATGACAGTTGCCATGAAGGAACCTTATAAAGCTC
 TCAGCCAATATATGGCAGATAATATTAATGTATAGCTTCAGAATATTGGAACATAAAGTAG
 ATTCATAATTTGCAGGATAAACAGGTCACCAGTTTAAAAACAGAAAAAAATCCCCACAAA
 AAAAACAAAAGAAGCGTAAGTACTTAACGTTTATTGTGTACAGAAATCTGTAGCAGATT
 CTGAACATATGGTAGGTTACATAGATGGTATATTATGCATATGGTATATATATAACATAC
 ATATTTACTTATGGACACATATTTGCCTAAATTGCATTAAGTTCTATAATATTACTGAGT
 AATAATTTTCCTCCTTTTCTGTATTGATACAGCATCTGTAAATGCTTATCAATAGGCAAA
 TGAAGTGAATATTTTGCAGATGTCTACAGTTTATCACTGTCTCCCTCACATCTATCACA
 TGTGTGGCGTA

The following amino acid sequence <SEQ ID NO. 95> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 28:

TPHIVIDVRETVINCRHLQNIHFICLLISYRCCINTEKEENYYSVIL*NLMOFRQICVHK*ICMLYIYH
 MHNIPSM*PTICESATDFCDTINVKYLRFFCFGDFLFLNW*PVYPANYESTLVPIF*SYTLILSAI

YWLRAL*GSFMATVIVSLGTRIYEGFYFKHLLHILI*NALHNVTF*QSTLEVPITYPFNPACMKS*
HTHFISMKMSLLEDHF*SLYKY*KSMIPLTI*LTA

The following DNA sequence nGPCR-Seq1039 <SEQ ID NO. 29> was identified in *H. sapiens*:

CTTTTACAGTGGGTGGCAGGGCTATGGAGGGGAAAACAGCAATGGTTCTGGCACCTACTT
AACTTGATTCCATTAAATTCACCCAACAGGCCTCCAGAGGAAGATATTACTGCTTTGATA
TTACAAAGGGAAAAACAGCTATGGCGTCTCTGAAAAGCACAACGTGCTAGGACTGGAATG
ACTTTAAAACACACATAAATTTCTGAGAGATTTTGGCATAAGGTACCATCCACCTTAC
TATAAACACATCCTAAAATTGTCTGCAGTGCAAATGGATTATGTGCATCCAACAGGAAA
CAGCATAGGTTGAGAAGCTGTTACTTAATAGCTTCATTGTCAACACGAGTGTAAGTGTG
GGGTCTCATCACTTTTGCACCCACGTTTGGCCTGTTGGTTTCTCCACACTGTCAGGAGCA
TTTGACCAACTCACTGTGGCTCAGGGTCCCTTACGCAGCCTGTTGGGGAAACCAGTGGGT
ATTGAAGACCTGCCTCTGGTGTGCCAGGAGGTTGTGCCTGCCGGCCACTCTGACTTGTGA
TCTTCCGCCTCAGTGTATGGCTTCTACACCTGGGTAATTAACATTGCCAGCATGATAAG
GAGGTCCTTTCATCACTATTGCCACTAGTCCTTCCGACTTCTGTGCCCTGTTTCTTCT
TTATTGGAACCAAGAACGAGTAAACATAGCATTTCAAACATCCCGCCCCCTT

The following amino acid sequence <SEQ ID NO. 96> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 29:

FLQWVAGLWRENSNGSGTYLT*FH*IHPTGLQRKILL*YKKGKNSYGVSEKHNVLGLE*L*NHT*I
SERFLP*GTHLTINHLKLSAVQMDYVHPTGNSIG*EAVT**LHCHHECKVWGLITFAPTFCLLVSP
HCQEHLTNSLWLRVPYAACWGNQWVLKTCLWCARRLCLPATLTCDLPPQCMASYTWVINIASMI
RRSFHHYCH*SFRLPVPCFFLYWNPRTSKHSIFKHPAP

The following DNA sequence nGPCR-Seq1040 <SEQ ID NO. 30> was identified in *H. sapiens*:

CTGTAATGCATACATAGTTCTTTTAAATTGAAGAGGAAAAAATGTAGAAATCCCAATAGA
AAAGAATGGGAAATAGATGACTAGACACTTCAGAGATGATCAACCCAAAATGGTAAACAT
TCCACATGAAAAACATTTTAAATTTACTAAGTCAAGGAAATCACAATTAAAGTGATTAAG
AGCTATCATATTAGTCTGTTCCAATATAAAATAGTAACACATTTAATATTGGCAGATATG
TAGGGGTCTTTGTATTTTAAACACCCTGATGAAAAAGTGTGAAGATTGGATGCCAATTG
TAAGAGTGTATATACAAAGATATTTATTGCAGCATTTTTTTGTAGGGTCCAAGAACTGAA
AATAAAGTGACTATCATTCTAAGGTAAGTGTATAAAATAAAATTAAGGGGTGAAAAGAGT
TCAGATACAAAGAGACTTGAATTTTTTATAATTGCTTTATTTTGAATAAAAATAAAT
AACACCTTTAATTCTTAAATTAATCTGGGATGTATTGTGTTTATACTATTAGTTTTTATT
TTCTCTAAAATGTATTTATGAAACCAACTTGATTGCATATACTAAATTTTTCAGTTCAA
TATCTGATAAGAGATGTCCCCAGGGCTTTTAAATAACGTATACCTTGTAATCATA

The following amino acid sequence <SEQ ID NO. 97> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 30:

FYFIQLPXNDSHFIFSSWTLQKNAAINIFVYTLLQIGIQIFTLFHQGVKIQRPLHICQYXMCYYFILEQ
TNMIALNHFNCDFLDLVNLKCFSCGMFTILGXSSLKCLVIYFPFFSIGISTFFPLQFKRTMYALQ

The following DNA sequence nGPCR-Seq1041 <SEQ ID NO. 31> was identified in *H. sapiens*:

TTGGAGAAGTGAGGTGAACTAATGTTTAGCTTACTATAGGACACAGATGGACACATATAG
AAGTATTTACAGATGTGAGTATATACATGGAATTAGTATACACACATATTTCTTTGCTCT
GTCAGTTGTCAGAGCCTAGAAGCAACAACAGTCCAGTGGCAATGGGCACACTTGACACCC
AGATCTTGATTTCTAATACCATTCTCCAATAAAAGGAACCAAGGGTTACTAGAAAACATAA
CTAATTCTAGGACTGGAGTAGGAAATATACAAGATGAACTGGGAGCATCTTGTAGTACCA
GGAAATAAGAAAGTTCTCAAAGAAAACCAATAAACAAACACCATAACATGGAATGATGGTG
GTATGTCAAAAAGACCCAAGAGCTGACTGAAAGAGCTTTAAATGGCCAAAGCTGAAACAA
TTTTAGCAACAAAATATGGTAGTATTCAATTAATAAGTATAAAATAAGTATCTAT

TAGTCCACACTGATAAAAAATGATTAAATAAATACATGGGCCAGAATAGAAAAATATCTC
GTGAAGAATTTCAAATAATTTATGTAAATACTCTGCCCTTAAGAATACAGATCATAACTC
TCTGCTT

The following amino acid sequence <SEQ ID NO. 98> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 31:

SRELXSVFLRAEYLHKLFEILHEIFFYSGPCIYLIIFYQCGLIDTYFILCILIEYYHILLKLFQLWPFKA
LSVSSWVFLTYHHHSMYGVCLLVFFENFLISWYKMLPVHLVYFLLQSN

The following DNA sequence nGPCR-Seq1042 <SEQ ID NO. 32> was identified in *H. sapiens*:

CAGGCAGGGGCAGGGGAAAGGTACAGCTGTGGAGGAAGTGACCAGGCCCAAGCAAGTGAC
GGTGCAGGAACACGTGCAAATTCCACAGCCACTGGGATGCTAGCACAAATAAGTGTGAGA
AACACACTCCCGGCTGGGGTGTGAGTGCCTGAGAACCACAAACGTACCTCCGTCCTGCCT
GCATTCATGTATCCCTATTGCATTCAAGTTGCCAGTACTCACCACCAAATACATCTACAA
TGCCCAATTTAAACCAATGTACTGGAAATGTCATTGAGTGCCAGGGGTACACAGAACCT
GCAGCCCAAACCTCTCCAGGCTCCTCAAGGAAATATCTGGCTCCAACTTTCTTTTAATT
ACTGAAAATCCCAGATGCTCCACATATAGAGAGATTAACAGATGCTCCAGGGGACAAGGT
CTATGAACATGCAATTACCCTACAAATTCATAGTATTAGTTCTTGGTTTAAACAGATTTC
CTTCTTTTACCCAGTTGAAAAGCATCTCTGGAAGTCAGAAGTAGTAAGTGGTGTTC
CTCCATTTCATCTCTGCCCCCAAATAAAGAAAAAAGTCTCTCTGACTTATTTTCT
AGCTCCAGGTCAA

The following amino acid sequence <SEQ ID NO. 99> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 32:

LTWS*KISQRDFFFFFFIWGQR*NGGKTPSYF*LPEMLFNWVKEGNLFKPRNTNMTNL*GNCMFIDL
VPWSIC*SLYMWSIWDFQ*LKESLEPDISLRLERFGLQVLCNPWHSMTFPVHWFKLGIQVDFGGE
YWQLECNRDT*MQAGRRYVCGSQALTPQPGVCFSHLFVLASQWLWNLHVFLHRHLLGPGHFLHS
CTFPLPLP

The following DNA sequence nGPCR-Seq1043 <SEQ ID NO. 33> was identified in *H. sapiens*:

TCATAGGAGGCTGGTGAGAAGGTAAATTGCCTTTGGTGTGTTGGAATGCAATCTGTTGT
TATTTGTCAAAATTTAAATGCATATATTTTGACTCACAAATACTTCTTTTAGGTATC
TGTCCCATAGAAATGAAAGCACAAAGGTATATTTAGGACAGCATTATTTTATGGGTACAAA
AGAAAACAAGTAGAAACAGTATGATTGCCCATCAATAGGAGAGTCATTGAATAAATTACA
ACATATTGCAATATAAAGTGTACACAGTTGTTAGAAAGAGTTATTGTTCGAGTAAGAAAA
AGCAAGATTTAAAAATATGTGTATGTTCAAATTTTGTCAAGATAATGACAAAACCTCTCT
ATGTGTATACTTATATTCATATATACATTATAAATATGTATATACAATATGTATAGTGGT
TTTTTTATGAATACAAGCATAAAAATATGAAAGTATATACAGTAAGTTGTTAGTATGGAT
AACTTTTGTGTCTATGAGGAAAGAATATAGATTGAGAGGGAGGTATATGGGAAAGGAAAA
GCTAAACCAAAATACAATACTGCAATAAAAAATTGTATGTATGATATGATCACACTTATT
GGAATTTATGTAAAATTATATGCAAGTATATGTATGTGTAAATATTTTAGAAGAAAAAA
TTACAAACAGAACAAGAAAAG

The following amino acid sequence <SEQ ID NO. 100> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 33:

LFLFCLXFFSSKIFTHTYTCIXFYINSNKCDHIIHTIFYCSIVWFWSFSEPIYLPNLYSFLIDTKVIHTNN
LLYILSYFYACIHKKTTHIVYTYLXCIYEYKYTHREVLSSLCKNLNIHIFLNLAFSYSTITLSNNCVT
LYIAICCNLFNDSPIDGQSYCFYLFVPIK

The following DNA sequence nGPCR-Seq1044 <SEQ ID NO. 34> was identified in *H. sapiens*:

GTTCAAAACCTTCTCACCTTGAATCTCTAGGTAAGATTTAGGTGCTGTCATCCAAGCATG
 CCATCCATCTAGGGACAATGCTGTCAATTTTCAGAGTGAATTATAGAATGAATTTTGTGTCAG
 CCAGTGATCAGCAGAGAGAAAGAGTGTTAGAAAAATCTTTATAGAACTTAAGAAGTGTGTCAG
 ACGTGGATAAGTGGAATGGAATTTGGATGGAGTTCTGGGTTAGACAGCAGGTAAGTTGTG
 CCTAAGTGCTGTTGAGCAAAGTGTTTGCATAGGAGGTATAGCTGTGTTTTCTGACAGTG
 AGTTTTCCAAGGCTCCACCATATCTTCCACCCCTCACACCAGCAGACTGCTAACCTATAA
 AACCATTTTTTCTACCAAGTCCTTACATGGCCTGGTAATGATTCTTAAAACAATACTTTG
 GCAACCACTGCCACAGGAAGGTAGCAACCCTCCTCAACTAAAACAAAGAAGTTGCTTCGG
 GAAATAGTAAAGTGAAAGTGCAGGGAGCAACTGGCAAGGGGCCTTAGGTTATAAGTTGAAT
 CATGTAAGTATAGGCCAACGTAAATGTAGGCTAGGACCTCTGGATGGTGAGATAACGAAA
 GGGACCAATCTCAGAAACACTGGGATACAAGA

The following amino acid sequence <SEQ ID NO. 101> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 34:

SCIPVFLRLVPFVISPSRGPSTLHLRWPIVT*FNL*PKAPCQLLPALHFTISRSNFFVLVEEGCYLPVAV
 VAKVLF*ESLPGHVRTW*KKWFYRLAVCWCEGWKIWWSLGKLTVRKTQLYLLCKHFAQQHLGT
 TYLLSNPELHPNSIPLIHV*HFLSFYKDFSNTLSLLITG*QNSFYNSL*N*QHCP*MDGMLG*QHLNL
 T*RFKVRRF

The following DNA sequence nGPCR-Seq1045 <SEQ ID NO. 35> was identified in *H. sapiens*:

CCCCCAGAGCGCCGCAGACTCGGGCCTGGAGCATCCTCTGGGGACAGGGAAACCACTCTC
 CCCGCAGTAGGAGGGGTCCCAGGAATTGAAGCTCCACGGGAAATTTCTGGTAGTTGGAG
 TGGAGTCTCGGCGGCTCCTCCGAACACAGCAATCGGTGAGTGAGTGGGACTGAGAGGCC
 ACGAGGAGTCCGAAGGCCAAAGCGTACACGATAGAGAGGAATAGTACGTAGGAGCTGGAG
 CAGTCCACCAGGCAGCCCCAGGGCGTGCGCACGAAGGCGCCCCAGCCGCACAGCGGGAGC
 GCCGAGAGCAGCAGACTGGCTGCCACACGGTCAGCACCAAGCCGAGCACCTGGCCCGAT
 CTTCTGGAGGCTGTCTGGCTCCCCACACCTCTGTGCATCGTATAAAAGTTGTAAGAGACT
 AGGAGAGTCGCCTTCAAGTTGCTAGAGAGGCCCTGGCATAAATACATTAAGGCAGAGGTG
 GTGCACAGAAATTGGAAGTAACCGGGGACCTCGTTTGGCCACTGCAAAAACATGAAGATG
 GTCACCGACAGGACGCTCATGAGATCATCCACAGACCAGGAAGCCACAAGCATGGACACA
 ACAGTTCTGTTCTGCATTTTCAGCAGGGAAATTAGTGAATAAATGCTGCCACCAAGGCT
 GCAAAAGTCATGAGACATGTCAAGCAAAAAAGATAGATATTTTCAGG

The following amino acid sequence <SEQ ID NO. 102> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 35:

NIYLFCLTCLMTFAALVGSISLISLLKMQNRTVVSMMLVASWSVDDLMSVLSVTIFMFLQWPNEVP
 GYFQFLCTTSALMYLCQGLSSNLKATLLVSYNFYTMHRGVGSQTASRRSGQVLGVVLTVAASL
 LLSALPLCGWGAFFVRTPWGCLVDCSSSYVLFSLIVYALAFGLLVGLSVPLTHRLLCSEEPRLHSN
 YQEISRGASIPGTPPTAGRVSLSPEAPGPSLRRSG

The following DNA sequence nGPCR-Seq1046 <SEQ ID NO. 36> was identified in *H. sapiens*:

GAAGAGGCAAAATGAAATGGCCACTTATATGGTATATGGTATATGGATCACTTGTTTCTG
 TTGAGTTACAGGACTCAGCTGGCTATTTCTCCCAATGTTAGTTATTTGGAGAAAAAACG
 TGATGGTAATTTTGGAGTAACAAATACAATATTTGATGAAAGCAAATTTATTGAGGGTTA
 GACAACTACAAGATACTTTAAGCTGCAAAGTCAACACGAGACTTCTGGCCCAAATTGTG
 CAGAGTTTGCCTCAGCTGCAAAGTTCAAAGGAAGAGGCCATATAAGACGATTCTCACTT
 CTGACACCAACTGCCAGTTCAGGGGTTTCCCCTGAACACACTCAGTTTCAAGAATTTACT
 AGAAAGACTCACAGAACTCATTGAATGCCATTGTACTTACGGTTTATAATAGAGAAAGGG
 TAGAAATTAGGACCAATTGGAGAGACATATCATATAAGGTGGAATCTAGGAGATTTTGAA
 TATTAAGTTTCCATTGTCTTCAGGACATACTACCTGTAATTGTTGTACAGCAATAAACAT
 GTAGTACTACCAAGCTGGGGAGCTCACCTGATGCTAAAAAGACACTATTTAGAGAATGAA
 AAGACAAATGAAAGGATGGGATAAGATGACCTTCCACATTAAGGCACTGGAAAGAATAAA
 AACTAAACCTAAAGCAAGCAG

The following amino acid sequence <SEQ ID NO. 103> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 36:

LLALGLVFYSFQCLNVEGHLIPSFHLSFHSLSNSVFLASGELPSLVVLHVYCCTTTITGSMS*RQWKLN
IQNLLDSTLYDMSLQLVLISL*TVSTMAFNEFCESF**ILETECVQGKPLNWQLVSEVRIVLYG
LFL*TLQLDANSAQFGPEVSC*LCSLKYL VVCLTLNKFAFIKYCICYSKITTTFFSPNN*HWEK*PAES
CNSTETSDPYTTYHISGHFILPL

The following DNA sequence nGPCR-Seq1047 <SEQ ID NO. 37> was identified in *H. sapiens*:

GGCCCCCTCCTCTACACTTCTGCCCTGTGGGGAGTCCCGGAGGCTCCATCACAGGCTTC
GCCGCCATGCCCTCTGGCTGTGATGCCAAAGTGCAGGGCAGGTAGGCATCGTGGATGACC
TGTCGGACAGTGGCCCGGAAAGTCTTGCTGACAAAGCAGTAGAGGCCGAAGTTGGCTGCC
GTGTGGAGCATGGCCACCATATTGGCCACATCCAAGGCCAGGTGGACCCCTCCAGTCCCGG
TGGACAGGGGGCCACGTACATGTGGTAGAGCATGACGAAGACCCGGGGCGCCACAGGAGG
GTGAACAGTGTGGTGTGATGCCCAGGAGGATGGCTGTGCTCTTGCCCAACCGGGGCTGCAGC
CCACTCCGGGCCCTCCTCCGTAGCCGGTGGATGATGGCCGAGTTGGTGACCAGGAACACG
CCACAAGGGATGAAATAGACAGTGAGACAGTGAGCCCACTTGAGGACCTCGTCCAGTGTT
CTGGGTGAGTCGGTGTCTCTCCACATGTCCAGCCACCAGTAGAAGGGGATGCCGGTCAA

The following amino acid sequence <SEQ ID NO. 104> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 37:

LTGIPFYWWLDMWRDTPRDLDEVKWAHCLTVYFIPCGVFLVTNSAIHRLRRRGRSGLQPRV
GKSTAILGITTLFTLLWAPRVFVMLYHMYVAPVHRDWRVHLALDVANMVAMLHTAANFGLYC
FVSKTFRATVRQVIHDAYLPCTLASQPEGMAAKPVMPEPPGLPTGAEVXRRG

The following DNA sequence nGPCR-Seq1048 <SEQ ID NO. 38> was identified in *H. sapiens*:

ATACGTTGGGAATTATTCTACACATACAGTATAGAAAAACCAGTAAGAAATATAAAATGT
TTCATACACCACAGTTTGTCTTCTGCTAGAAGACACACAATGCCCTCTCATGAATCTA
TGGAGATGAAGGCTTCTCTCCTTTCACCCAGTACCTCACTTGCCGCAAAACTGAAAGAAA
AGTCTGCTTTAGCTTCTTGTTTCCCCAAATCAGGATGAATGGGTGGATTGAAGGATAGCT
GAATCTAATAGCTTTGCAGAACATGAAGACAGGTTTGTCTTCCAGACTCCCAAACTCCA
AACTGATATCATTATGGACAGAAAGTAAACGGCACATAACAAGAGGAAAAAGATCACAGT
TTGCAAAGCTTTTATGTGGACCTTGGTGTGCTGGGATCTTGAGATCCTTTACCATGGAGCTG
CATCTTCTTGAGATGTTTACACAGAGAACAGATTAACAGCAAAAAACATAGCAGGGTCAG
AGTGAAGGGCACTAAGTTTCTAGCGTGGTTACAGTCGCATCTGAAAGGTACACTGCACT
CCTCAATTGATCTTCCAAGTCATGTTTCTTTCATATTCTTTTGTCCGTACAATCTCTTT
CATGTTTATCACAAAAAGTTGACAAGCCAAAAATAGTAAAGGCCCAACAGCATCACCAG
AATGACACTCTTAACCTCTCCTC

The following amino acid sequence <SEQ ID NO. 105> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 38:

RRVKSIVLVMLLGPLLFLACQLFVINMKEIVRTKEYEGNMTWKIKLRSVYLSDATVTTLGNLVPF
TLTLLCFLLLICSLCKHLKMKQLHGKGSQDPSTKVHIKALQTVIFFLLCAVYFLSIMISVWSFGSLE
NKPVFMFCKAIRFSYPSIHPFILIWGNKKLKQTFLSVLRQVRYWVKGEKPSPXIHERGIVCLLAEN
KLVVYETFYISYWFFYTVCE

The following DNA sequence nGPCR-Seq1049 <SEQ ID NO. 39> was identified in *H. sapiens*:

TTTATTTCAAGCTCTAACTTATTTTAAAAATAAGTGTTTTTATAAAATTTTGAAAGGTC
TGAATGTCTAAAAGAATTGGCTTAAATTTTAGCAATTTAGTTTGAGACATTAGCCTAACA
ATTTCTAGCTATGTCTGAATGTATGATTGGCATTCCAAATCTGTGATATTTTCTTACCT

TTATTTTAAAAACATTAGAATTGCTTTGTTCTTGAATCTTGGGGGTAAATTTAGAATC
 AACTTACTTTCTTGATTGTCTCAAGCTTTTAAATTTGCAACTCAAAAATAAGGTGTGCAT
 GTGGTTTTGTCTAAACTGGGATAAAA
 CAGAGCTGGGGAAAAATACCCTGTGACGGCCCCCTAAAAGAATAAGTGGGTTTGCATTAGC
 AAGGCTCTTACACAACTCTGAATCAAAGAGCCACAGAAGCTTGTGAGGCAGAAATTCTC
 TGAATTGTCACACTGTGAACAGAGGAAAGCCACATAAAGAAAGTGATGCCGCTCTTGGGC
 CAAAAACTACCCA

The following amino acid sequence <SEQ ID NO. 106> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 39:

G*FLAQRHHFLYVAFLCSQCDKSENFCLNKLWLFDSELCKSLANANPLILLGAVTGYFSPALFY
 PSLDKTTHTHTHTHTHMHTLFLSCKFKSLRQSRK*VDSKFNPDQSRKQF*CF*K*R*ENITDLE
 CQSYIQT*LENC*ANVSN*IAKI*ANSFRHSDLSKFYKNTYF*NKFRA*NK

The following DNA sequence nGPCR-Seq1050 <SEQ ID NO. 40> was identified in *H. sapiens*:

TTGGCTGGGGGGCCGGGGAGAGCATGGGTGGGGGTGCTGGTTTGCTTGGTTTATAACACTT
 CTTCTTGCTCCTCAATGCCAGGGCAGAGAGTGTGCCCCCTGTACATGCATCCTTATTTGTG
 GGCAAGGCTCCGTCCATGCAGGTGCCTGGAGATGTGGGTTTACTCACACATTCCCAGGCT
 CTCAGGGTTGGAAGGGACTTTGGAAGAGGCCTTCCCCCTCCTCCCTCACCTGTTCTGCCA
 TATCCATGCCAAATGCTCATCTGGATTCTGCTTGATCACTCCAGTGACTGGAAGCTCAC
 TTCTTCCCCAGGCAGCCCATCTCTGCTGACTGCTGGAATACTGAGCTGGAAACTGTGCCA
 GCAACCTGGACAATTCCCCACCCCTATCCCATCTGCATGAAAACGGGACCAGGACAAGA
 TGCCAAAAACACAGCACCTAAGATAGTTACAGCTCATGCTTACAGAATACCTCCTTAGC
 CAGGCACTGTACTAAGTGCTTTACGTATCTTCACTCTCATAATCTTCATGAAACTCTAT

The following amino acid sequence <SEQ ID NO. 107> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 40:

GWGPGRAWVGVLVCLVYNTSSCSSMPGQRVCPCTCILICGQGSVHAGAWRCGFTHTFPGSQGWK
 GLWKRPSSSLTCSAISMPNAHLDSA*SLPVTGSSLLPQAAHLC

The following DNA sequence nGPCR-Seq1051 <SEQ ID NO. 41> was identified in *H. sapiens*:

TCATAATCATGAGACTCTTCTCCTCGGAGTTTCCTTTCAACAGGTGGGACATGGGATGCT
 GTGAACTGCTCCTGGGACACGTTCTCACTGGGTCCCTTCGCCTTCCCTGTCAGGTGACACC
 CTCCGCATGCCATCATAAGCCTGGTGACCATCTCTGGGGGAAGAGCTTCCCCGACGTGG
 TTCTGCCGGGGACAAGCAGAAAAATATGGTTAGACAGTGCACAAGTTGAACTTGGTTACT
 AGGAGTTATTATTTTAGGCAGATAGAGAGGAAAAGGGGTCCCTTGGGAAGTTTTCGTTTTT
 TAAAGCATCTCTGAAAAAGTTTCTTGTAAGCCCCGTCTCTTAGAGCCAGGCCGGAAACT
 TTGATATGCAAATGCCGGCCATTAGAAACTGGGTCCACCCACCAAGGTGATTCCCATGGC
 TTCTTGCCCTTTCCCCACATGTTCTGGCAACATGGCCGCCTCCACATATCCCCACGTG
 TATAGAACATCCATGGTGCCCTGCATTTACTTATTAAGAGGCTAGGGTGGGAGGGGCCAGC
 TTTTTCATGGGCTACGTGAATGACATACCTGGTCAAACCAATCCAGAGCCCTGTGCAAAT
 CAGACATCGCCTCCTCCAGCCTCTGCATATATACCTGGCTGGTGTCCACCGCACTTGAGG
 ACCTCTTCTTTGGCTTTGGAGCT

The following amino acid sequence <SEQ ID NO. 108> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 41:

DSSPRSFLSTGGTWDAVNCSWDTFSLGPFAFPVRSTLRMPYSYSLVTISGGRASPTWFCRGQAEKYG
 *TVHKLNLVTRSYYFRQIERKRGPEVVFV

The following DNA sequence nGPCR-Seq1052 <SEQ ID NO. 42> was identified in *H. sapiens*:

CTCTGTGCAATGACACATGGGACTTATAGTAGACGGTAATATGCTGAAGAACTCATGAA
 AAAGTCTTAAATGATCAGCATATTTATTTATTTATTTATACATTGTTTCTTTTAATCAAA
 AAGTATATGCACATGATTAAGAAACAAAAATTTCTGAAAGGTCCAATAATTAATAATAAA
 TGAATCCTATCCTACTCACCCCATTTCTTCCCAGACACATTCTCTTTTAACTATTATTC
 TTGTTATTTACTTCCATATTATTAATAAAGTATACGAAATGTTGCTATTTCTCCTCATTTATC
 AGTTTATAGATCATATTTATTTTCTGCCATGATATATGGGTTTATACCTGTTTCTTGGTCC
 TTTATGGTCTCAGTATTGTTATAGCACCATCATGTTCTTCGGCTCTGGTAATTTTTCTGC
 TTTCTTTTACAATTTATTCTGTTTTCTCTCTGGAATCCGTTTTTTTTTTTTTTTAGAA
 ATTGGCACTCC

The following amino acid sequence <SEQ ID NO. 109> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 42:

LLFLVIYFHIIKKYTKCCYFLIYQFXIIFICHDIWVYTCFLVLYGLSIVIAPSCSSALVIFLLSFTIYSVF
SLESVFFFFRNWHS

The following DNA sequence nGPCR-Seq1053 <SEQ ID NO. 43> was identified in *H. sapiens*:

CATGTGGTAATACATGTTAGAATTCCACTGCTTTTCAATATGGAAGCTTTTGAGTTACTA
 CTTACTTGTGTTGAGTGTGGAATTAATTGTTTCTATTGTAATTATTTAGTGGAAAGTTGAC
 CCAATTATAGAATCAGCTCTTTTTATTTTAATGTAAACATGATTAAATGACTTTCTGTC
 TGAATAATGAGTTGTTGCTAAACTAATTGTTGGATTAAAGTCCAGTTTAAACATCGACGCC
 ATTGATAATGAAAGACCTTGAGCTGTCAGCTAATTTTCATGACATTGTGTAGCGCCTGCT
 TTCCTAAAGTCTGTGGGATGTTGCGGAAGCACACTTCCAGTTTTTTGTTTCAGATATTTA
 ATTTCTGTTGGTCATAATATTGGGCATGTACCCATGGGCTGACATTGGCCATCTGAGATC
 CATGATTTCTCTCTATCTGCATTATAATTTATGTATTGTAATTGTATGTGGTTTACATCT
 GCTGGTATGTATACGTCTTCTCTTTGATATGTTTGTCTTAGTGTGCTTCAAGTAGCAAA
 GAATTACCTTTTCTGGGTTAATAGCTTTACAACCTGGATTATATTCTCCGTGCTTAAACC
 TTAGCACTGTTTGATGCGTTTTCCCAACATCGTAAGGCTGGCAGATTGGCGTGTTCTTTC
 TTTTCAGTGTATGGAAGCACCAGGTAGCAATCCAGTTTTAATTTTCTGCCTGTAA

The following amino acid sequence <SEQ ID NO. 110> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 43:

FLLVILGMYPWADIGHLRSMISLYLHYNLCIVIVCGLHLLVCIRLLFDMFCLSVLQVAKNYLFWV
NSFTTGLYSPCLKPXHCLMRFPNIVRLADWRVLSFQCMEAPGSNPVLIFCLL

The following DNA sequence nGPCR-Seq1054 <SEQ ID NO. 44> was identified in *H. sapiens*:

CAACAATACCTCTGTATCCTGTACTGCTGGAGCCACATCTCAGCACGGTAGCCTGTTTTG
 GTGGCTCGAGGAAGGGCAATCCAAACTGCACTGTGTTCAAGTGGCGGGTCGCCAGGTTGCT
 GCTGTATAGGAAACCCAGCTAGATTTGGAAGGAGGCCAGTGACTGCAGTGAGAAAAGCAG
 ACGGGACTGTTGTGAGGCATAGACGTTGAACTTGCATCAGACTCTCTGGATCATCGTGTC
 TAGATGGCTCTGCAACCAGCACTTGCTGTGCGGAGACAGTTTAGCGTGTGACCGCTGGGG
 GTGAGCGACTAAACCTCATGGTCTCTTGGGATTCCAGCATTACGCTGCCTGTGCCAATA
 GAGGAATCTTCAAACCTCTTTATTGGCTTCTCTCTCCCTCATCTAAAGTGAAATAAAGTCG
 TCTTTGAAATGGATTGGAAGAAGAAATAATTTGCCTACATTTCCCAAAGTGGATATTCA
 CTGGTGGAAATGTCTGCAGTTATCTGGGGGTGGATCTTTGTCATGGACGGCCATTAGCAT
 CTCCTTGGGAAACTGTCTCTGAACACAAAACATCTCCAGTTTTGTAGATCAGTTTTGACA
 GACTAACTGCATGTGAATTTCAAGAGCCCCAGTTTGTA

The following amino acid sequence <SEQ ID NO. 111> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 44:

RVTAGGERLNLMVSWDSSIHAACANRGIFKLFIGFSLPHLK*NKVVFEMDWKKK*FAYISQKWIFT
GGNVCSYLGVDLCHGRPLASPWETVSEHKTSPL

The following DNA sequence nGPCR-Seq1055 <SEQ ID NO. 45> was identified in *H. sapiens*:

GCCCCCTCCTTCGGGGCGGCCCTGTTCCCTGCAGGCCGGCTCGGTTTCACCTTCCCAGGA
GTGGCTGCCAGAGCCCAACAGCACTCTCCTTCCGCCTTGGGTTCTGGGAGAGTCTGATGGC
CTCTGAGGACAGGGATTTATGGATCTAGTATTGTTCTGACCAGGGAACTTGATCTTCC
TTCCTACCACCTCCAAAGTCACCTTTAGGCAGGGCAGGCAGGGACCGGGGCTGGGTGAGC
TGTGTCTGGTTTGGTGTCTGGCTGGTGTCCAGCCCCAGGCTCCAAGTCTGGGTCCAGGCCC
CTCCCTTCTCTTCCCTGCCACCTCCCTGGGTCCCTGGTCAGCTCCGATTGCTCCTGGCT
TGGGAGAAGTCCTAGGTGCCTTGTGGCAGCCTTCACTGGTGTGAGTTACTCCTGCTTCCC
CGGCGCTCACGTGGCCCCGGCCACCTTAGATGAGGAAGGACGCTAACCTGGCAGA

The following amino acid sequence <SEQ ID NO. 112> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 45:

WPLRTGIYGSSIVPDQGNLIFLPTTSKVTFRQGRQGPGLGELCLVWCRLVSSPRLQVWVQAPPF
LFPATSLGPWSAPLAPGLGEVLGALWQPSLVSVTPASPALTWPRPPLDEEGR

The following DNA sequence nGPCR-Seq1056 <SEQ ID NO. 46> was identified in *H. sapiens*:

TCTCAGCTGTTGCTTACTGCTTAAGATAAATCATCACACTAATGTCCTTTATTCTTTTCA
GTTGCTATCACTTGATACATCATGCCTGGCTTTGAACAAAAAATTATGAGACTTGCTAAA
AAGCAGAAAAAACAACATTTTGAAGAGAAAATCAAGTTTAGAATCAGATTCAAATG
TAACACAGAAGTTTTAGAATAAGATTTTAATGTAACAGATTTTCGATCAGACATGACATTT
AAAATTACTATGATAAAAATGTTAAGATTCTGGTTGAAAAAATAGACAAAATGCAAAAGA
AGATTTAGCAAAGAGGTGGAAATTATGTGAAAGAATCAAAAGGATATGTTAAATATCACA
AACACTGTGATAGAATTAATAAATTGCTCTGAGGGGCTGATCAGTACACCAGAAATTGTC
TAGTAAAGAATCAATGAGTTTTAAGATGGCTCAAAAAAATCAGAAGCTAAAATGCAAAG
AGAAAAATGAATGAACAAACAAGCAAACAGACAAAAAGACAGAATAGAACCAAGAATATG
GAAATATTTCAAAAATGGAATGCATGTTTGATTAGTAAGACAGAAGAAATATTT
GAAGTAACAATGGCCAAGAATTTTCCAGAATTAATAATAACTAAACACAGATCCAGG
AATATCAGAGAACATCAAGCAGGATAAATACCCACATTTATAT

The following amino acid sequence <SEQ ID NO. 113> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 46:

YSWICVLVLLILENSWPLLLQIFLLSYYSNQTCIPVFEIFPYSWFYSVFLSVCLFVHSFFSLHFSFXFF
LSHLKTH

The following DNA sequence nGPCR-Seq1057 <SEQ ID NO. 47> was identified in *H. sapiens*:

GCTGCCTTGCCCATGGAAATCTTGGTAATTGATAACTTCTCCTTTTCTTGAAGCCAGGGG
AGGGAGGACACGCCAGGTGGCCCTGGCAGGGCTGGGCTAGCTCTTCTTGGCTGCTGGGAG
CACTCATTGATGCGTTAATATAGCCCAGGTACAAGGACTATGTGGCGAGGTGGAGAGAAG
CCGGAGCCTGGGAGCTCAGCCACTAGATAACCCCCGAAGTTGGCAAGTCTCATTCTTGGC
TGCTCCCTCCTCCCCTCAGAAAGTAAGGTGGCTCCCAGGAGCTGTTGGGCAGGGAAGAC
CAAGATATATGGCCCTTTCCACGTGGGGGCTGCTGTCTTCTTGTACCTCTATTTCCAG
TCAATGTTTAGCTATTCAGCCCTCCAGGCAAAAAACAACAAAGCACAAACCACTTTTG
GATGTGTAG

The following amino acid sequence <SEQ ID NO. 114> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 47:

RVKRRQPPRGKGHISWSSLPNSSWEPPYFLRGGGRQPRMRLANFGGYLVAELPGSGFSPPRHIV
LVPGLY*RINECSQQQGRASPALPGPPGVSSLPWLQEKEKLSITKISMGA

The following DNA sequence nGPCR-Seq1058 <SEQ ID NO. 48> was identified in *H. sapiens*:

CAGGTTTTTGGGTGGGTGATTTTCCCTTGTCTGTCCAACCGTCTTTATCCACAAAGGATT
CCAGCTTGTTTGTAAATAAACCAGATCCCTGAATAAGGCAGCCTCAGGCCCACTTTATAGG
CCCATTATACCAAGCAGGGTAGGGAGCAAAGAAGAAAAGCTACAAAATAACCAGAAGGG
AACACAAGAAGGGAAAGGAAATGTGTGTGTGTGTGTGATATCTTCTGTCTCTCTGAAA
ACACAATTCCCTGCTCACTTGTGTGGCCTCTTCCGAAATCAGAGCCTCTCTTCCTTTTCC
TATGCCTCTAATCTGTTTCTTCTCTCTTCCCTTCTGTCCTTTGCCTATTTTTTTTTTTT
TTTTGGAGATGGAGAGAAGTGAGGAACTGGAAGTTATACTGTGTGTCTCCAGCAGTGTC
CACAGTTGAAATAATAATGGCTAATATTCAGGAGACAGTTATGATGTTCCAGAACTGCAT
CAGAACTTTCCAGAGAATATGGTATGTTTGGCGAGGGGGCAGGACGTTATGTAACATGGG
AGCATAAGATGTGAGGAGGGCAGAAGAAAGACGCTGGGTGCCAGTGTGAC

The following amino acid sequence <SEQ ID NO. 115> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 48:

RHRKRKRGSDFGRGHTSEQGIVFSEQRORYHTHTHISFPFLCSLLVSFVAFLLCSLPCLVXWAYKV
GLRLPYSGIWFTTNKLESFVDKDGWTDKGKSPTQKP

The following DNA sequence nGPCR-Seq1059 <SEQ ID NO. 49> was identified in *H. sapiens*:

GCGATTTGGCAGTAGGTTGTACCAGTTAGTACAAATCATCATCTTTCTCTTCCTTACCCC
ATGTCGGCAGACCGCGGCCAGGATGCGGGATCCCAGGGCGCCAGGCGCTCCCATCTGCTC
TGCTGAACAATGTGTGGTCCACCCTTTATCCAAGCTGCAGAGGGGAAGGGCAGATGGAGC
CACCTTGCCTTCTAAGTGACTTCAGCAAAAGCACATCTGTCCTCCAGGGCAGGTTCTCGA
CCCCAGCACTATTCACATTTTATAGCTGGATCGCTTTTCGTCGTCGGAGGCTGTCTTGTTT
GTGGTGGGTGTTTATAGCCGCACCCCTAGCTTCTACCCACTAGATGCCAGTAGCACCCCTC
CCAGATATGACCATCAAAAAATGTCTCTGAACATTGCCAAATGTCCCTGGGAGTGGGAGG
CACAATCACCCCCTGTTGAGAACCACTTAGAAAGAACTTTTGCTGGGAAGAGCTCAGAGC
ATGCATTTAAACAGTGTTTCGGTGTTCTCGCATTAGCCTTTCCCAAGGGAATTAGTTACTA
ACTGAATGTCACCTTCTCCACGAGACTTCCCCTGAGCACCCCTATTTATGCTCACTCACTA
TTTTCACTTATCATGTAACTGTTTAAATATTCTGCCTCCCCTGTTACACTATATGTA
GTTCCAGGCACAGAGTAAATGTTCAAAAACATTTGTTGGCCAGGCAAGGTGGCTCATGCC
TA

The following amino acid sequence <SEQ ID NO. 116> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 49:

RFGSRLYQLVQIIIFLFLTPCRQTAARMRDPRAPGAPICSAEQCVVHPLSKLQRGRADGATLPSK*L
QQKHICPPGQVLDPSITHIFSWIAFRRRRLSCSWWV

The following DNA sequence nGPCR-Seq1060 <SEQ ID NO. 50> was identified in *H. sapiens*:

AAGCACACTTTACTCTCTCCCACTGAAGGCAGCTTTCAAACCTTGGAAGAATGTATGCAG
TAGTATTTGAAGATGCTGAAAAGTCATTAGTAGCAGACAGACTGGGAAAGGAGACCAGAA
TTTGAAGTACCACTGAACCAGCAGTGAGTTTATCCTTTTTTTTCCCTCTAGTATACCCA
GACTGAATTCAACACATTCAAAAGCCCAGTAGTGAGTATTGGGGTGCATACAGAGAAAGA
TCCAGGAAAAGCCTCTCAAAGGGTGGGAAAAAGAACTCCTAATACTCAGAGAGAGTGTGA
AAAATCCCCCATTTTTTCCACTTTCTTTTCTCCATTTACTCATACCCCAACCTCCGGGCA
ATCCTGTCGTGATGGCAGTGAAAGCAGCAGCAGCTGCAGCACCAAGTAGCAACGGGAATCA
TCAGAAGTCAAAATTCTGAAAAAGGGAGACTTTCCTCTCTTTTGGTAGAGCAGTAGTTCT
AAGAGGATGAGACCAATTCTCACTCTGTCTTTTCTGTTTTCCTGCTGCTTGGACCTAGA
TATGCAAGTATACATCAGAAAGGGGTAACTGTTCTAAGTTTCTGGTGAGAGAAC

The following amino acid sequence <SEQ ID NO. 117> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 50:

EAFPGSFSVCTPILTTGLLNVLNSVWVYXREKKRINSLLVQWYFKFWSPFPVCLLMTFQHLQILL
HTFFPSLKAAFSGRE

The following DNA sequence nGPCR-Seq1061 <SEQ ID NO. 51> was identified in *H. sapiens*:

AACTTTTGGTTCTGGAAAAAATTTTGAATTATTTCCCTGGTAATTTCTTCCTGTCTGTTC
 TCTTTCCAGAACTCCTACTATTTGGATGTTGAGCCTCCTAGACTGATCTTTTCTCTCAAT
 ATCTTTGATACTGTGGCTTTATGCTTTGTTTTATGCATTTTCGGTCATTTTACATAATTT
 CAAGCAGTAATGGTAAATGCATATGTCCAGTCCTCTGCATTTAACTGGAATCCTCTGATC
 TCTTTTCAGATACTTTACTGCAGGTAAGGAAACTATTGTAGAAATCCATATGGCATGTCT
 GAGATGAGCACCAGGCTTTTTTTTTTTTTTCTGGTCTGATTCTCCCACTTATCAAACCTCT
 TCTTTAGGATATTTACACTAAGTAGAAACAAAGGCAAGTAAATGAAAGTAGAGCAGGACC
 AGGTGCAAGCCCCTTGGGCACATTATCCACCTTCGCTGTTGCTAGGTTTACTCATTTTCAG
 AGATGAAGGCCAATAATACCCACTTTTATAGCTCAAGCTTGTCTTGATGAACAAATGAG
 GGCATGTAGATGAAGA

The following amino acid sequence <SEQ ID NO. 118> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 51:

CAQGACTWSCSTFIYLPFLLSVNILKKSLISGRIRPEKKKKA
WCSSQTCHMDFYNSFLTCSKVSEK
RSEDSSXMQRTHMHLPLLEIM

The following DNA sequence nGPCR-Seq1062 <SEQ ID NO. 52> was identified in *H. sapiens*:

TTGTGGTTGGTGATTCAGGGGATCTTCATTTTTGCTGTTTTTCTTTTCCAGAATGGCTTT
 GACTACTTACTAACATACAGTGACAATCCCCAAACGGTGTTTCCTCGCTACTGTGTTAGT
 TGGATGGTTTCCAGTGGTAAGTAAGGGCAAGTATACAGGGCCTGGAACCTGGGTTGAGCA
 TTTTGTTTTTCTCTATTTCTAATGGGGAAATAAAACGTCTCTTCTGGTTCTTCTTTTTT
 TTTTTTTCTGAGACAGAGTTTTCAACAACCCATGCTTTGGGAACACATTCCGGGAGGCAG
 CTCTTATTCACAGGCTAGTCAGGTTGTGATCTTTATAAGGAAGAACTAGTTCCTACCAT
 CAAAGAAATAGGGTCTTCTCATTTTGAGCCTACTGTTGGTTTGTATGTCAGCTTAACCTG
 ATTCTCGTCTCCTGACAGGCATGCCAGATTTCTTGAGAGAAGCTGCACATGGCCACTCTGA
 AAGCCAAGAATATGGAGATTAAAGTAAAGGACTACATCTCAGCTAAGCCTCTGGAAATGA
 GTAGTGAAGCCAAGGCCACCAGCCAGTCCTCTGAGCGAAAGAACGAGGGCAGCTGTGGCC
 CTGCTCGGATTGAGTATGCTTGACAGGC

The following amino acid sequence <SEQ ID NO. 119> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 52:

FRGSSFLLFFFSRMALTTY*HTVTIPKRCFLATVLVGWFPVVSKGKYTGPGTWVEHFVFLYFLMGK
*NVSSGSSFFFFSETEFSQPMLWEHIPGGSSYSQASQVVFIRKN

The following DNA sequence nGPCR-Seq1063 <SEQ ID NO. 53> was identified in *H. sapiens*:

ATTCTGCCTAACACACACATCATTACTATCTTCATCTTCATTATCATCATTACAAAGCAG
 TTGGATTACCCAGAACCATGCGTAGTTTGCATATCACATGACTATAAAAGGTAATTTTAC
 AAAATACGATGAAATCTAGCAGAAGTGGTTCTAAAGGAATGACGAGAGGACAATTTACTT
 GGTAAGGTGGCCAGTTGGCAAGACTGAGAAACTGGTTGCAGTGACAGGAATCACATTTCT
 GAACCAAAGCAAAACATCAAAAGGCCGTGGTCTGACAAATGTGAATACTTAAATGGACA
 TTAGGTGAGCATACTGGGAAGATGTAAGAGGGGGAAGTGGCCACAGTTGTAGAAGCAGATT
 TTGGGGTGATACCATTGAAGTAAAACTTAAAGGCTACTATGCCAAAGGGCCAATTTAACA
 AATGGAAAAAATATGTATATTTCAAAATGTCAGACCTCAAGGAGAAAGGTTTGTGACAAA
 TTAAGAGTGTGAGATTTGAATATTTTACACTAATAACCACAGTGTTTCATTCCTCAGTAG
 TGAATCATTTTGTCTCTCTCCATACCAACCCCATCTCTCTCACACAGACACACATGCTC
 CCTAGTACCCAGGGCTCCCAGGACTCATGCCTTGGGAAGTGAGAGGACTCAGCCCCGAAT
 CATGAAACTC

The following amino acid sequence <SEQ ID NO. 120> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 53:

VFTFVRPRPFDVLLLVQKCD SCHCNQFLSLANWPPYQVNCPLVIPLEPLLLDFIVFCKITF
YSHVICKLRMVLGNPTAL

The following DNA sequence nGPCR-Seq1064 <SEQ ID NO. 54> was identified in *H. sapiens*:

GTGGCAGCGGTACTAGGATGGGCCACAGGGATGGACAGGCAGTGCTTGGTGCTGATGGAG
CCCAGCATGCTCAGGCCTGTAAAGTAGAGAAGGTCATCACAGTGGTGAAATAGGTGGAGA
TGGAAAGGAAGAAGTCATGGTAGAAATTCACAATTTCTAAAATCTGGGAGCAGAGGAAGA
AGTCGGCCCCCGGCCAGGTTGAGGGTGTAGAGGGAGAAGGTGTTCTGTGCATGCGGAATC
CCAGGAGCCAGAGGAAATGACTGCATTTCTGCCAGCTGGACCAGGTCAACGATGAGGAG
CAGCAACATGAGGATCATGATCTCCATGCCACAATGTTGAAGATGGGTCTCCTCGGTCTT
ATTGATTGATGTCAGTTCTGTACCCAAGGCTGGGATGGTTGGATCCATGCACAGAAACCC
TAGTCTGGTGCCCCCTGGGAACACAAAAAAGATGTGATCAGCAGCTGTGTGATCTCTGATT
TCACATACATTCTATTATATGAGAATTATTGTCCCCATTTTACAGAGGAGAGAAACAGGC
TTGCAGAGAATAAGCCACCTGTCAAAAGGTGAGGAGTGCTGAACTCCAGTTTCAAATCCA
GTTCTTGGTGACTCTAAAGCCTGGGCTCTCTCTATTGCAACACAATTTTCTCTACTGACA
TGGGAATAA

The following amino acid sequence <SEQ ID NO. 121> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 54:

LLPFHLHLFHHCDLLYFTGLSMLGSISTKHCLSIPVAHPSTAA

The following amino acid sequence <SEQ ID NO. 136> is another predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 54:

PGPAGRKCSHFLWLLGFRMHRNTFSLYTLNLAGADFFLCSQILEIVNFYHDFFLSISTYFTTVMTF
TLQA*ACWAPSAPSTACPSLWPILVPLP

The following DNA sequence nGPCR-Seq1065 <SEQ ID NO. 55> was identified in *H. sapiens*:

TTTTGTGGTTTAAAAAATATATACAGCCCTGTGGTTCAATCAGAAGCCTGTTACTTTTA
CATTTCCAAATTTATAATTTACTACACTTACGTGACTCCAGCGAGCATTATATAAGCAGCA
AAGCTCTTGTACTTAAAAGCACTGAATCATTTTATCCACAAAAGAACCCTATTAGGGAT
GTAATGAGATTTTGAAAATTAAAAAAGCTCAAGCCATTGACTTATAATGGTTCGC
AAAACAGATCACATTAGATGAAAGATGCTTGAATCTTACTTTTCAGTTTCTAGGTTATTA
TTTGTTCCTCCAGATTTTCAGGAGGCAAAGCGAGTGAGAAGACAGGCAGGAAAGGGACACA
GGGAGCTTCTGCAGAGATGACAACCTCCTCTCTCTAAAGGGCACTGTCATTCCCAAGGGC
ACCACCAATCCCAAGGCTTCAGTCCCTATGAGACTATGGCTGCTTTTGTGGCATCCATGG
GTGAAAACCTGGCCTCAGCTGGCATGGAGGCTCTCAGTCAACAGCTGCTATACCTCCTCT
TTTAGCCGTGCAGCCTAAACTCACCAGGCAATTTTCATGCTTTGGTTCAAGTGACAAAA
TCAGTGTTTGAAAGCATATCAGAACCTTGACCTCTTGCACTCTCATTCGGGTCACCTCATG
ATTTTCAGTGGCTGAAACGATG

The following amino acid sequence <SEQ ID NO. 122> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 55:

EDRQERDTGSFCRDDNSSPLKGTVIPKGTTPNPKASVPMRLWLLWHPWVKTPQLAWRLSV
NSCYTSSF*PCSLNSPGNFHALVQVHKS FESISEP

The following DNA sequence nGPCR-Seq1066 <SEQ ID NO. 56> was identified in *H. sapiens*:

AATAGATTCCATAGTCACTGTGAGTAATTTTCTCCATTCAATTTTGTGATTGAGTGAAGT
 TTATTGTCTAGTAGGTTCTTCAGAAGTGTTTCATGGGAAGTCACATCTATCTGTTTCCTTT
 ATATTTAAATGACAGTTTGGCTGGATATAGAAATCATGGATCACATATTATTTTCCTGGG
 TTCTTTGTATCATATTTCTGTCTTCCAGCATCAAATATTGTTGTGAACTATAAGGTCAGT
 CTAATTTTCTTCTTTGTATTAAGTATGGGAAAGAACTAATACTGTAAACAAAGTACAAA
 AATACAGTGAGTTAACTAAGATTCAACCTTGTATCACTCTCATGTATCAGTCTGGCTGGT
 CTAAGTTATCAGAGCAACTGCTGCGCAAGGTCACCCAGAGAGCCATTTCTTCCATGTTGT
 TGCTCCACTATCCCTTTTTGGGCATTTTGTACCCCTCAAAATCAAAAGTGGGATGTTGGC
 AAATCTACCTTCCAGCTTGCAAAAGAGGAAAAGAGGGCAAAATACAGAGAAAGCAGATTTT
 CTTTAAATTGCAAATGACITTAACATACTTTTGTACATATTCAATATTCAGAACTTGCTCA
 TGGCCACCGTAGCTAACTGAAAAAAAAGCTAGAAAATGCAGTATCTAGCTGGGTGGCCT
 TAGAGTTAGAAATA

The following amino acid sequence <SEQ ID NO. 123> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 56:

QFGWIXKSWITYYFPGFFVSYFCLPASNIVVNYKVSLIFLLCIKYGKETNTVTKYKNTVSXLRFNLV
 SLSCISLAGLSYQSNCCARSPREPFLPCCCSTIPFWAFCHPQNQKWDVGKSTFQLAKEEKRQNT
 EKAADFL

The following DNA sequence nGPCR-Seq1067 <SEQ ID NO. 57> was identified in *H. sapiens*:

GAATTGGCCTAGGGTGGGGCTTGGCCATGGGTCACTTTTCAAAGCTCCTGAGCAATGCTG
 GCACCCATTCATGGTTGTCCGCACTGGGGCAGCAGTTTCGGCCATCTGGTAGGAACAGA
 GCACAAAGCTCCACCTATATCCCAGCTGCTGGCTAAGGAAAATGAACTGTTCCAAGTCA
 GATTTTTTTTTCAAGCTCCTCTCTAGACAAAGGAGAAGATAATAAAATAAAAGAGTTAA
 AACTAGAATATGAGACATTTGGATTGGATATAAGAAGAACTTGGGGGAAGAAGAGGTTA
 GGTATTAAAATGTATGACCTCAGGGATATTGTGTTCATATCATTTTCTGGAGGGTTTCACA
 ACAGGGATGAATTTCCATCTGTCTTCAAGGTGTTTCTAATGGAATGTCAAGATGATACTG
 GAGACTATAGCTCATTCTTTTAGACAGGGCTGAATTCTGCACTTATTCATTGAAAATAAA
 TCAAGTTTTTCCCAAGTGTCCTATAATGTCCTAAAAAAGGGCACTAGGCTGGATGAAGGA
 TTTGGGTGTACACATTGTGGCGGGTCTGTTTGTAGAACTGTGACAGGCAGTAGAGT

The following amino acid sequence <SEQ ID NO. 124> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 57:

NWPRVGLGHGSLFKAPEQCWHPFMVVRHWGSSFGHLVGTEHKAPPISQLLAKENETVPSQIFFFK
 LLSRQRRR

The following DNA sequence nGPCR-Seq1068 <SEQ ID NO. 58> was identified in *H. sapiens*:

CTTTATGATCAGTTCTCGAATGCCCTGCCTTCTCGTTCTCAATTCAGTATCCTTTCCATT
 GTTCCTTGCTGTATATTATTGGCCAGCCAGTCTGGATGGAGCGGCAGGGATGGTTCAAAT
 AAATGAAGGCCATACCAAAGTCATCCTATTGAAGGCTCATGTTGGGCTTAGGCCAGAGCT
 CACTGATACTGAGATGTCCCTTATTCTGTGTCTCTTTCACTGTCTATGGTATTACTCTGC
 TTTCACAGAAGAGCGAGTCTTGGGGAACAGAAACACCCGTATCATCCTAGTTCAACAGCT
 TCTTGCAACTCCCAAATTTACTTATTTCTGCTCCTGCTTCTTTCATTGATCTAGCTGC
 CAGTGAAATATTTGCTGCTTCTCAGTGACCTTTGTATTTGATATGAATTGTTTATTTTCA
 CTTTAAAGTTGAAATATAATTTGTATATTATAACAATATAACCATTTAAGGTGTACAATTC
 AGTGGTTTTTAGCAGTCAGTTGTGCAGCCATCACAATTTGACAGTATTTTCTTTCCCCCT
 AGAAGAAACACCATAACGAATTCATTGTTACCCCATTTCCCCCTTTTCTCCAGCCTTTCAC
 AACGACTAATCTACTTTTCTCTA

The following amino acid sequence <SEQ ID NO. 125> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 58:

FMISSRMPCLLVLSVSFPLFLAVYYWPASLDGAAGMVQINEGHTKVILLKAHVGLRPELTDTEM

SLILCLFHCLWYYSAFTEERVLGNRNTRILVQQLLATPKFTYFLPPAFFIDLAASEIFAASQ

The following DNA sequence nGPCR-Seq1069 <SEQ ID NO. 59> was identified in *H. sapiens*:

CAAATAGTACAAAACATCTGGAGGTGACATTATAAAGGGGTCAGTGTTTGACCACCAGCC
AATGGAAAAAGTTATATATATAGAAAATATATTCTATGTATCCCATTGGATGTATTTTCT
CCTTTTACTCATGCCTCTCTGCTGGAGTTCCATATTCCTGATTTTCTCACTGTTGCCCTT
CATGACCATGAAACCTTTGTTCACCCATCCATTCCCATTCTTTCAAGTACTCTTTGAAG
TTTATTAAAGCCACTTCTCTCACAGTCGTTTTAGATTTTCCCTTAAGTAGCCTCTAAATC
TGCAAGTCCCTGACCTTGGTCATTCTGGTTACTCTAAAGTGGTGCCTGTAGATAACAGAT
ATTCCAATGACTATATCTAGCTTAATGATTCTCAAATTATTCACATGGGCAGTCAGTATC
ATGAGGTCCTTGGGGAGTCATCATGAAGATGACTAAAAATTCAAATAAATGGTGAGAGTC
AC

The following amino acid sequence <SEQ ID NO. 126> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 59:

PPANGKSYTYRKYILCIPLDVFSPTFTHASLLEFHIPDFLTVALHDHETFVHPSIPISFKYSLKFI
KATSLTVVLDLPLSSL*ICKSLTLVILVTLKWCL

The following DNA sequence nGPCR-Seq1070 <SEQ ID NO. 60> was identified in *H. sapiens*:

ACTTCTTCATGTCTTTGGCAACTTTGTTTAATTTTTTTAAAGTTGCTAGTCTCTTTTTCT
TAATGAACGGTCCTTGTTTCATGTTTCGTGGCCATTTTCATGGTCAGCCGTCTGGGCAAGC
TGCTTTTTCTCTTCTTGTGGTATCACTCCTCCTCTCCTTACTGCTCAGCTGTAGTTTCAC
ACAACAAGCTAAGTGGAGCTCGTGGGGTCACTTACAGGAAACAAGGAGCATGACTCGCAC
CCATGAAGTTAGAAATGGCACACGGGGAGGGGAGATAGAGCAGATCCGTGCACAGCACTC
ATGTGTAAAATATGCCTGCACCACTGTCTGCTTTGCGTTTGAGTTCAAACAAAAGGCTT
CCGTGAAATATAATAAGCTATATATATTTTTTCAGAGTGACAAGAATTGTCTCGCTTCCCT
TCAGTTCCCAGACTTCTCCAAAGTTAGTCTAATGTCATGACATTGCCTGGGGAGGCCAGA
GGCTGGCCTCAGAGACGAGAAAGCAGGTAGCTTGGCTTGGGCTTGTTTCTTAAGGGTCTA
GGTGCCTACAGCGTAGAAATTCAGCATTTGCAGAGCACCCGAGGTGAGGGGCTGGGGGAC
GGCAGAGCC

The following amino acid sequence <SEQ ID NO. 127> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 60:

FFMSLATLNFNFFKVASLFFLMNGPCFMFVAIFMVSRLLGKLLFLFLWYHSSSPYCSAVVSHNKLSGA
RGVTYRKQGAXLAPMKLEMAHGEGR

The following DNA sequence nGPCR-Seq1071 <SEQ ID NO. 61> was identified in *H. sapiens*:

CTTTTAATAATTTTTATAAATCCCAAACATTATATCTTCATATTTATTCTTTTTCTCTTC
TCAAGTTTCAAATTTAGTTACACCATTTAAAATGCATTTTCCATGGCTTTGTTTTTTTC
TCACTTTTAATTTCAATTTTGCTTCAGTTGAGTACTTTCCATTGGTCTATCCGTCACTGTC
CCTGTTTCTCAATTGTGTTGATTTGAGAGTCAACTCAAAGGCATTTTTATCCTTTTTA
CTGTGTTTACATTTATATCATATTCATGTCCTTCTTATTATCCTCGAGTCTCAGCTGATA
GTAGTCATTTCTTTATGCATGTTGTTTCATCTTCACTGTAACATTTAACACAAAAATTATA
TCTATATTGAATCCCCGGTTTAATAATTCCAACACCTGGATCATTCTGAATCTGATTCT
TTTGATTGCTCTATTTCTTGACAGAGTGTGTTTTAATGCTTGATCCTCCACAGTTTAATT
ATTATTGGCTGACTGTCAGATTTCTTTTGTGTTGACAGTAGAAATTATAGTATATATTTT
TATTCCTGAAAATAGACATTCATTTTTT

The following amino acid sequence <SEQ ID NO. 128> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 61:

FNNFYKSQTLYLHIYSFSLKQIXLHHLKCFHGFVFFLTFFNFILLQLSTFHWSIRQCPCFLNCVDLR
VNSKAFFILFTVFTFISYSCPSYYPRVSADSSHFFMHVVHLHCNIXHKNYTYIESPV

The following DNA sequence nGPCR-Seq1072 <SEQ ID NO. 62> was identified in *H. sapiens*:

AAAAATAAAAGCACCTTGTTCCATGCAATTCGTATGGGAAAGTTTTGGGTGTCAAAGGTC
 GCTGGGGGATAGATGGGGAGGCAGAAATAGCTTGGGAAAAGGAAGCAGGAAAAAAGGAAA
 TCTTTATGGGAAATCAATTACCCAAAGCAAGGTGAGTCACCTAGAGGTGAATATGATGTT
 GTTATTGTCCTCCCTTAGTGTACAGCACAGTTTTTGTCTCACAGGGTTTTTCTCTTTAG
 GATGCGTAGCACCTATGCATTAAATACATAGCATCCTAAAGACACCCTACTCACCATGA
 GTCTGTAGGCTCTTTCCTGATGAGGGCACTGGCCATATATGAATGGAAAACCTCAACTCAT
 CTCCTCAGCTTTAGATGTTGCTGCTGTTTCAGCTGGATTTGTGAGAAATATCTGGATTACT
 ATCAAGAACATTTAGCAAGACTCAAAAGAGAGAGGCAAGCAGAACCAAAACCCAAACCTC
 AACCAATGACTAGCTGAATAAACAATTCTTTGGAGGAATAAGGAAGGTATTTCTGGATGT
 ATTCTGAGAATGCTCTTCCAAAAGGGAAGATGGTAATAATGGACTTGTTTTGATTTCATG
 GTTGTGATAGAATGTACTTCCATGATGTGAAATACACTTCTGGCAGATAAAATGCAGGTT
 GTAATTTGCATTTGTACATCACAGGG

The following amino acid sequence <SEQ ID NO. 129> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 62:

PCDVQMQITTCILSARSVFHIMEVHSITTMKSKQVHYHLPFWKSILRIHPEIPSLFLQRIVYSASHW
LRFGFWFCLPLSFESCXMFLIVIQIFLTNPAEQQQHLKLR

The following DNA sequence nGPCR-Seq1073 <SEQ ID NO. 63> was identified in *H. sapiens*:

AGGATGGTGATTGAGGATGATGTTGAAAATTGCTTAGGGGAAGTTTTTCAGAGGGTTTTGT
 GGCCTTATTTTTGGCAGTGGGGAGAATGAGAAGTCACCCTGGCTGAGATGAGAAGATAGG
 GGAGAGTTCTGAGCAGAAGTGAGGCGTTGCCCAAGTTGCTGCGGAAAAGGTTACCTGGG
 TGCCTGTGCGCAGGTGGGCCAGAAAGTACGCAGGTGCACGAAGAAGGAAGCCCGTGAGCA
 AGGCAGGGTGGCTCAGACCCCCAGTGGCGTAGACCAAGGCGGCAGGGGCACAGGTTGGGAG
 AATTGGATTTTGGATCTGTTTTGAATAGGGACTCCACTGAATGCATTGTTGGATTCTCTG
 TGTGGTGTGAGATCTACAGAGGTCTAAAAATGGCTCCAAAAGTTTCATCCTGACAGCCTG
 AGCCACTGGCAGGATGGAGTTGACTTTACCAAAACAGGGAAGATGTCAAGGGGGCCAGGA
 TTGGGAAAAGCATGAACAAGGACTGTGGTTGAGTTTCAGGTGTTGAGTTGCCTCTCTGCA
 TCTCTGCAGCAAAGCAGAGACATCA

The following amino acid sequence <SEQ ID NO. 130> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 63:

ISHHTENPTMHVESLFKTDPKSNSPNLCPAALVYATGGLSHPALLTGFLLRAPAYFLAHLRTG
TQVNLFRSNLGNASLLRLPYLLISARVTSHPHCQK

The following DNA sequence nGPCR-Seq1074 <SEQ ID NO. 64> was identified in *H. sapiens*:

TTACAAAGTGGCCTGTAAACAAGGCCTGTCATGGGAGGAATCATCTAGGTTTACTAACAG
 CACATCAAACCTGAGATGGAGAAGTCCCATGCCATATATGACAGATCTACCAAGCTGGCTT
 TACAAAATTCATCTATGAAGACCCACAATCCTCCCCTCCCCACACCTAGGGCTTTGCCAG
 TCTAAAGGTTTCAGCCAAGAAAAAAGGTGCCCACTAGGACTGTCCTTGATTCTGGGAA
 CATCCTTCAGGAAGACATCCCAGGCTATTAGCCATGTGAAGTTGGCCACTTGCCCCTGGT
 AACTACCACAAATAGCCCTTGTTGAAAATTCAGCTAACTCCTGATTATCCACTCAGTTCC
 GGAAAGGCACAGATAAACCTCAGAGTGAGTAATTACCAATATCTGGCTTTGGAATGCAA
 TCTTCTGAAATAAAAAAATACTTACATCTTACCTCTGTGTAGGAGGTTTTTTTGGTTT
 TTTTGTGTTTGTGTTGAGATGGAGTCTTGCTCTTGTCACCCAGGCTTGGAGTGCAGTGGCA
 CGATCTCAGCTCACTGCAACCTCCGCCTCCCCGGTTCGAGCAATTCTCCTGCCTCAGCCT
 CCTGAGTAGCTGGGACTACAGGCACAC

The following amino acid sequence <SEQ ID NO. 131> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 64:

QSQILVITHSEGLSVPFRN*VDNQELAEFSTRAICGSYQGQVANFTWLIAWDVFLKDVPRIKD
SPSVAPFFSWLNL*TGKALGVGRGGLWVFIDEFCKASLVDLSYMAWDFSISV

The following DNA sequence nGPCR-Seq1075 <SEQ ID NO. 65> was identified in *H. sapiens*:

ACTCTAGCTCAGAAAAGCCTTAATATCTAGCATGGACAACCCATAGGCCCGGTGGCTCTT
GTACTTTTACAACCCCATTCCTAAAACCCACAGACCAAAACCTGAAGGCTAGTAAGGAGG
AACATGAGTCAACAAATGACCTCATTCTCCATTTGTTTACAACTCCACTGATGTCTGTG
GTTTCCAAGTATCATTATTTTAAAAATGGGTGAAATAGTGTGAGATCTCAGAGCACTTT
TCTTTTCTCTCTTTTCTTTTTCCTTTTTTTTTTTTTTTTGAGACAGTCTTACTCTGTC
TCCCCAGGCTGGAGTGCAGTGGCGAGATCACAGCTCACTG

The following amino acid sequence <SEQ ID NO. 132> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 65:

AVISPLHSSLGRQSKTVSKKKKKRKKEKREKKSALRSHTISPIFKIMISWKPQTSVEFVNKWRMRSF
VDSCSSLLAFRFWSVGFWNGVVKVQEPPLWVHARY

The following DNA sequence nGPCR-Seq1076 <SEQ ID NO. 66> was identified in *H. sapiens*:

CAGTCCCATCAACAGTGTAAGGTGTTCCACTATGAGATAGCATCTCACACCAGTTAGAA
TGGCAATCATTAAAAAGTCAGGAAACAACAGGTGCTGGAGAGGATGTGGAGAAATAATAT
CTTTTTTAACCTTCTTATACATAAATAATTATGGTGACTGAGAGAAAAAGAACAATCAAG
AAAGAAGATCCTCAGGTCATATAAGTTAGATTGAAAATAATGTCCTTTTGTTCAAATAAGA
AAGGTAGGCAGGAACCAGCAGTGGTGATGAAAATGGTGGCTCTGTGTATTTGTGGGCCAT
ACAAATCAGAAAGGTGAATGTTCTGAGCTCCAGAGAAATCTAGAGGAAGATAAGAGTT
GGCTTATCAGCATAGAGGTGGTAGGTGAGGACAGGGGATGAAATAACACACAAAATATAT
AAAGGTAAGTAGAAGTTGAATATGGAATTCTAAGTGATTGGGAGATTAAAAAAAATGACA
CACAGAAAAGAGTGAACCAGGTCACATAGAAAAACATTGCTTTCTTCAAAGACAAGAAAG
GAGACAGTTTGAAG

The following amino acid sequence <SEQ ID NO. 133> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 66:

FKLSPFLSLKKAMFFYVTWFTLFCVSEFLISQSLRIPYSTSTYLYIFCVLFHPLSSPTTSM LISQLLSSS
RFLWSSRNHLSDLYGPQIHRATIFITTAGSCLPFLFEQKTLFSI

The following DNA sequence nGPCR-Seq1077 <SEQ ID NO. 67> was identified in *H. sapiens*:

TTTTGCAGTCTTTTTGTCTTTATGCTCCTCTAAATTATTTCCAGTGATCTGTCATTGGAT
TTGCTAATCCTTTCTTTTGTCTGGTCTAGTCTGCTGTGGAACCTCTCTAGTAAATTTTTC
AGTGTAAGTTGTTTCAGCCCATGATTTCTGTTTGGTACTTTTTAAGATTTCCCATCTCGTT
GTTGAAATTCTCACTATATTTTTGTGTCTTGTATGAGCATCTTGTAATTATTTTAAATTA
TCTATTGGATAAATCATGTAAGGTTGGTTTCTGTATGTTTATCTTGTTCTTTGTTTAGA
ACATTTTACCTGATTCTTCATTTTTTCTTGACCCTCTATGTTGGTTTCTGTATATTAAC
AAAGCAAGCACCTCTCCAGTCTTCATGGACTGGTTTTATAAAAGAGAACACTTTCACCA
ACAAATACAGCCAAAAATAATGGTGGCCTATAATAATTCTTTCCCTCCTGAGGAGGAATT
AGGCAGCTGTGATTTTTGTCCATTTATTCTGTGTTGAGCCAGAGAGAGGGTAGCTATGGT
CTACAAGCCCAAAACACCATTTTCATACTTCTCTGAGCAGCTTGACTGTGCTGGGCCTGC
TTAAGTCAGCACTGGTTAGAAATGCTAGTT

The following amino acid sequence <SEQ ID NO. 134> is the predicted amino acid sequence derived from

the DNA sequence of SEQ ID NO. 67:

FAVFLSLCSSKLFPVICHWICXSFLLLGLVCCGTSLVNFSVYVVQPMISVWYFLRFPISLLKFSLYFC
VLDEHLVIIFNYLLDKSCKVGFCMFILEFLCLEHFYLILHFFLTLYVGFCILTKQAPLPVFMDFWYKR
EHFHQQIQPKIMVAYNNSFPPEEELGSCDFCPFILC

Example 2: Cloning of nGPCR-x

cDNAs may be sequenced directly using an AB1377 or ABI373A fluorescence-based sequencer (Perkin Elmer/Applied Biosystems Division, PE/ABD, Foster City, CA) and the ABI
5 PRISM Ready Dye-Deoxy Terminator kit with Taq FS polymerase. Each ABI cycle sequencing reaction contains about 0.5 µg of plasmid DNA. Cycle-sequencing is performed using an initial denaturation at 98C for 1 minute, followed by 50 cycles: 98C for 30 seconds, annealing at 50C for 30 seconds, and extension at 60C for 4 minutes. Temperature cycles and times are controlled by a Perkin-Elmer 9600 thermocycler. Extension products are purified
10 using Centriflex gel filtration (Advanced Genetic Technologies Corp., Gaithersburg, MD). Each reaction product is loaded by pipette onto the column, which is then centrifuged in a swinging bucket centrifuge (Sorvall model RT6000B table top centrifuge) at 1500 x g for 4 minutes at room temperature. Column-purified samples are dried under vacuum for about 40 minutes and then dissolved in 5 µl of a DNA loading solution (83% deionized formamide, 8.3 mM EDTA,
15 and 1.6 mg/ml Blue Dextran). The samples are then heated to 90C for three minutes and loaded into the gel sample wells for sequence analysis by the ABI377 sequencer. Sequence analysis is done by importing ABI373A files into the Sequencer program (Gene Codes, Ann Arbor, MI). Generally, sequence reads of 700 bp are obtained. Potential sequencing errors are minimized by obtaining sequence information from both DNA strands and by re-sequencing difficult areas
20 using primers at different locations until all sequencing ambiguities are removed.

To isolate a cDNA clone encoding full length nGPCR, a DNA fragment corresponding to a nucleotide sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:67, or a portion thereof, can be used as a probe for hybridization screening of a phage cDNA library. The DNA fragment is amplified by the polymerase chain reaction (PCR) method. The PCR
25 reaction mixture of 50 µl contains polymerase mixture (0.2 mM dNTPs, 1x PCR Buffer and 0.75 µl Expand High Fidelity Polymerase (Roche Biochemicals)), 1 µg of 3206491 plasmid, and 50 pmoles of forward primer and 50 pmoles of reverse primer. The primers are preferably 10 to 25 nucleotides in length and are determined by procedures well known to those skilled in the art. Amplification is performed in an Applied Biosystems PE2400 thermocycler, using the
30 following program: 95C for 15 seconds, 52C for 30 seconds and 72C for 90 seconds; repeated

for 25 cycles. The amplified product is separated from the plasmid by agarose gel electrophoresis, and purified by Qiaquick gel extraction kit (Qiagen).

A lambda phage library containing cDNAs cloned into lambda ZAPII phage-vector is plated with *E. coli* XL-1 blue host, on 15 cm LB-agar plates at a density of 50,000 pfu per plate, and grown overnight at 37C; (plated as described by Sambrook et al., supra). Phage plaques are transferred to nylon membranes (Amersham Hybond NJ), denatured for 2 minutes in denaturation solution (0.5 M NaOH, 1.5 M NaCl), renatured for 5 minutes in renaturation solution (1 M Tris pH 7.5, 1.5 M NaCl), and washed briefly in 2xSSC (20x SSC: 3 M NaCl, 0.3 M Na-citrate). Filter membranes are dried and incubated at 80C for 120 minutes to cross link the phage DNA to the membranes.

The membranes are hybridized with a DNA probe prepared as described above. A DNA fragment (25 ng) is labeled with α -32P-dCTP (NEN) using Rediprime random priming (Amersham Pharmacia Biotech), according to manufacturers instructions. Labeled DNA is separated from unincorporated nucleotides by S200 spin columns (Amersham Pharmacia Biotech), denatured at 95C for 5 minutes and kept on ice. The DNA-containing membranes (above) are pre-hybridised in 50 ml ExpressHyb (Clontech) solution at 68C for 90 minutes. Subsequently, the labeled DNA probe is added to the hybridization solution, and the probe is left to hybridise to the membranes at 68C for 70 minutes. The membranes are washed five times in 2x SSC, 0.1% SDS at 42C for 5 minutes each, and finally washed 30 minutes in 0.1x SSC, 0.2% SDS. Filters are exposed to Kodak XAR film (Eastman Kodak Company, Rochester, N.Y., USA) with an intensifying screen at -80C for 16 hours. One positive colony is isolated from the plates, and replated with about 1000 pfu on a 15 cm LB plate. Plating, plaque lift to filters and hybridization are performed as described above. About four positive phage plaques are isolated from this secondary screening.

cDNA containing plasmids (pBluescript SK-) are rescued from the isolated phages by in vivo excision by culturing XL-1 blue cells co-infected with the isolated phages and with the Excision helper phage, as described by manufacturer (Stratagene). XL-blue cells containing the plasmids are plated on LB plates and grown at 37C for 16 hours. Colonies (18) from each plate are replated on LB plates and grown. One colony from each plate is stricken onto a nylon filter in an ordered array, and the filter is placed on a LB plate to raise the colonies. The filter is then hybridized with a labeled probe as described above. About three positive colonies are selected and grown up in LB medium. Plasmid DNA is isolated from the three clones by Qiagen Midi Kit (Qiagen) according to the manufacturer's instructions. The size of the insert is determined

by digesting the plasmid with the restriction enzymes NotI and Sall, which establishes an insert size. The sequence of the entire insert is determined by automated sequencing on both strands of the plasmids.

Example 3: Subcloning of the Coding Region of nGPCR-x Via PCR

5 Additional experiments may be conducted to subclone the coding region of nGPCR and place the isolated coding region into a useful vector. Two additional PCR primers are designed based on the coding region of nGPCR, corresponding to either end. To protect against exonucleolytic attack during subsequent exposure to enzymes, *e.g.*, Taq polymerase, primers are routinely synthesized with a protective run of nucleotides at the 5' end that were not necessarily
10 complementary to the desired target.

PCR is performed in a 50 μ l reaction containing 34 μ l H₂O, 5 μ l 10X TT buffer (140 mM ammonium sulfate, 0.1% gelatin, 0.6 M Tris-tricine, pH 8.4), 5 μ l 15 mM MgSO₄, 2 μ l dNTP mixture (dGTP, dATP, dTTP, and dCTP, each at 10 mM), 3 μ l genomic phage DNA (0.25 μ g/ μ l), 0.3 μ l Primer 1 (1 μ g/ μ l), 0.3 μ l Primer 2 (1 μ g/ μ l), 0.4 μ l High Fidelity Taq polymerase
15 (Boehringer Mannheim). The PCR reaction was started with 1 cycle of 94C for 2 minutes; followed by 25 cycles at 94C for 30 seconds, 55C for 30 seconds, and 72C for 1.3 minutes.

The contents from the PCR reaction are loaded onto a 2% agarose gel and fractionated. The DNA band of expected size is excised from the gel, placed in a GenElute Agarose spin column (Supelco) and spun for 10 minutes at maximum speed in a microfuge. The eluted DNA
20 is precipitated with ethanol and resuspended in 6 μ l H₂O for ligation.

The PCR-amplified DNA fragment containing the coding region is cloned into pCR2.1 using a protocol standard in the art. In particular, the ligation reaction consists of 6 μ l of GPCR DNA, 1 μ l 10X ligation buffer, 2 μ l pCR2.1 (25 ng/ μ l, Invitrogen), and 1 μ l T4 DNA ligase (Invitrogen). The reaction mixture is incubated overnight at 14C and the reaction is then stopped
25 by heating at 65C for 10 minutes. Two microliters of the ligation reaction are transformed into One Shot cells (Invitrogen) and plated onto ampicillin plates. A single colony containing a recombinant pCR2.1 bearing an insert is used to inoculate a 5 ml culture of LB medium. Plasmid DNA is purified using the Concert Rapid Plasmid Miniprep System (GibcoBRL) and sequenced. Following confirmation of the sequence, a 50 ml culture of LB medium is inoculated
30 with the transformed One Shot cells, cultured, and processed using a Qiagen Plasmid Midi Kit to yield purified pCR-GPCR.

Example 4: Hybridization Analysis to Demonstrate nGPCR-X Expression in Brain

The expression of nGPCR-x in mammals, such as the rat, may be investigated by *in situ* hybridization histochemistry. To investigate expression in the brain, for example, coronal and sagittal rat brain cryosections (20 μ m thick) are prepared using a Reichert-Jung cryostat.

5 Individual sections are thaw-mounted onto silanized, nuclease-free slides (CEL Associates, Inc., Houston, TX), and stored at -80C. Sections are processed starting with post-fixation in cold 4% paraformaldehyde, rinsed in cold phosphate-buffered saline (PBS), acetylated using acetic anhydride in triethanolamine buffer, and dehydrated through a series of alcohol washes in 70%, 95%, and 100% alcohol at room temperature. Subsequently, sections are delipidated in
10 chloroform, followed by rehydration through successive exposure to 100% and 95% alcohol at room temperature. Microscope slides containing processed cryosections are allowed to air dry prior to hybridization. Other tissues may be assayed in a similar fashion.

A nGPCR-x-specific probe is generated using PCR. Following PCR amplification, the fragment is digested with restriction enzymes and cloned into pBluescript II cleaved with the
15 same enzymes. For production of a probe specific for the sense strand of nGPCR-x, the nGPCR-x clone in pBluescript II is linearized with a suitable restriction enzyme, which provides a substrate for labeled run-off transcripts (*i.e.*, cRNA riboprobes) using the vector-borne T7 promoter and commercially available T7 RNA polymerase. A probe specific for the antisense strand of nGPCR-x is also readily prepared using the nGPCR-x clone in pBluescript II by
20 cleaving the recombinant plasmid with a suitable restriction enzyme to generate a linearized substrate for the production of labeled run-off cRNA transcripts using the T3 promoter and cognate polymerase. The riboprobes are labeled with [³⁵S]-UTP to yield a specific activity of about 0.40×10^6 cpm/pmol for antisense riboprobes and about 0.65×10^6 cpm/pmol for sense-strand riboprobes. Each riboprobe is subsequently denatured and added (2 pmol/ml) to
25 hybridization buffer which contained 50% formamide, 10% dextran, 0.3 M NaCl, 10 mM Tris (pH 8.0), 1 mM EDTA, 1X Denhardt's Solution, and 10 mM dithiothreitol. Microscope slides containing sequential brain cryosections are independently exposed to 45 μ l of hybridization solution per slide and silanized cover slips are placed over the sections being exposed to hybridization solution. Sections are incubated overnight (15-18 hours) at 52C to allow
30 hybridization to occur. Equivalent series of cryosections are exposed to sense or antisense nGPCR-x-specific cRNA riboprobes.

Following the hybridization period, coverslips are washed off the slides in 1X SSC, followed by RNase A treatment involving the exposure of slides to 20 μ g/ml RNase A in a

buffer containing 10 mM Tris-HCl (pH 7.4), 0.5 M EDTA, and 0.5 M NaCl for 45 minutes at 37C. The cryosections are then subjected to three high-stringency washes in 0.1 X SSC at 52C for 20 minutes each. Following the series of washes, cryosections are dehydrated by consecutive exposure to 70%, 95%, and 100% ammonium acetate in alcohol, followed by air drying and exposure to Kodak BioMax™ MR-1 film. After 13 days of exposure, the film is developed.

Based on these results, slides containing tissue that hybridized, as shown by film autoradiograms, are coated with Kodak NTB-2 nuclear track emulsion and the slides are stored in the dark for 32 days. The slides are then developed and counterstained with hematoxylin.

Emulsion-coated sections are analyzed microscopically to determine the specificity of labeling.

The signal is determined to be specific if autoradiographic grains (generated by antisense probe hybridization) are clearly associated with cresyl violet-stained cell bodies. Autoradiographic grains found between cell bodies indicates non-specific binding of the probe.

Expression of nGPCR-x in the brain provides an indication that modulators of nGPCR-x activity have utility for treating neurological disorders, including but not limited to, mental disorder, affective disorders, ADHD/ADD (*i.e.*, Attention Deficit-Hyperactivity Disorder/Attention Deficit Disorder), and neural disorders such as Alzheimer's disease, Parkinson's disease, migraine, and senile dementia. Some other diseases for which modulators of nGPCR-x may have utility include depression, anxiety, bipolar disease, epilepsy, neuritis, neurasthenia, neuropathy, neuroses, and the like. Use of nGPCR-x modulators, including nGPCR-x ligands and anti-nGPCR-x antibodies, to treat individuals having such disease states is intended as an aspect of the invention.

Example 5: Tissue Expression Profiling

A PCR-based system (RapidScan™ Gene Expression Panel, OriGene Technologies, Rockville, MD) may be used to generate a comprehensive expression profile of the putative nGPCR-x in human tissue, and in human brain regions. The RapidScan Expression Panel is comprised of first-strand cDNAs from various human tissues and brain regions that are serially diluted over a 4-log range and arrayed into a multi-well PCR plate. Human tissues in the array may include: brain, heart, kidney, spleen, liver, colon, lung, small intestine, muscle, stomach, testis, placenta, salivary gland, thyroid, adrenal gland, pancreas, ovary, uterus, prostate, skin, PBL, bone marrow, fetal brain, and fetal liver.

Expression of nGPCR-x in various tissues is detected using PCR primers designed based on the available sequence of the receptor that will prime the synthesis of a predetermined size fragment in the presence of the appropriate cDNA.

PCR is performed in a 50 μ l reaction containing 34 μ l H₂O, 5 μ l 10X TT buffer (140 mM ammonium sulfate, 0.1% gelatin, 0.6 M Tris-tricine, pH 8.4), 5 μ l 15 mM MgSO₄, 2 μ l dNTP mixture (dGTP, dATP, dTTP, and dCTP, each at 10 mM), 0.3 μ l forward primer (1 μ g/ μ l), 0.3 μ l reverse primer (1 μ g/ μ l), 0.4 μ l High Fidelity Taq polymerase (Boehringer Mannheim). The PCR reaction mixture is added to each well of the PCR plate. The plate is placed in a MJ Research PTC100 thermocycler, and is then exposed to the following cycling parameters: Pre-soak 94C for 3 minutes; denaturation at 94C for 30 seconds; annealing at primer 57C for 45 seconds; extension 72C for 2 minutes; for 35 cycles. PCR productions are then separated and analyzed by electrophoresis on a 1.2% agarose gel stained with ethidium bromide. The 4-log dilution range of cDNA deposited on the plate ensures that the amplification reaction is within the linear range and, hence, facilitates semi-quantitative determination of relative mRNA accumulation in the various tissues or brain regions examined.

Example 6: Northern Blot Analysis

Northern blots are performed to examine the expression of nGPCR-x mRNA. The sense orientation oligonucleotide and the antisense-orientation oligonucleotide, described above, are used as primers to amplify a portion of the GPCR-x cDNA sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:67. Multiple human tissue northern blots from Clontech (Human II # 7767-1) are hybridized with the probe. Pre-hybridization is carried out at 42C for 4 hours in 5xSSC, 1X Denhardt's reagent, 0.1% SDS, 50% formamide, 250 mg/ml salmon sperm DNA. Hybridization is performed overnight at 42C in the same mixture with the addition of about 1.5×10^6 cpm/ml of labeled probe. The probe is labeled with α -³²P-dCTP by Rediprime™ DNA labeling system (Amersham Pharmacia), purified on Nick Column™ (Amersham Pharmacia) and added to the hybridization solution. The filters are washed several times at 42C in 0.2x SSC, 0.1% SDS. Filters are exposed to Kodak XAR film (Eastman Kodak Company, Rochester, N.Y., USA) with intensifying screen at -80C.

Example 7: Recombinant Expression of nGPCR-x in Eukaryotic Host Cells

Expression of nGPCR-x in Mammalian Cells

To produce nGPCR-x protein, a nGPCR-x-encoding polynucleotide is expressed in a suitable host cell using a suitable expression vector and standard genetic engineering techniques. For example, the nGPCR-x-encoding sequence described in Example 1 is subcloned into the commercial expression vector pzeoSV2 (Invitrogen, San Diego, CA) and transfected into Chinese Hamster Ovary (CHO) cells using the transfection reagent FuGENE6™ (Boehringer-Mannheim) and the transfection protocol provided in the product insert. Other

eukaryotic cell lines, including human embryonic kidney (HEK293) and COS cells, are suitable as well. Cells stably expressing nGPCR-x are selected by growth in the presence of 100 µg/ml zeocin (Stratagene, LaJolla, CA). Optionally, nGPCR-x may be purified from the cells using standard chromatographic techniques. To facilitate purification, antisera is raised against one or more synthetic peptide sequences that correspond to portions of the nGPCR-x amino acid sequence, and the antisera is used to affinity purify nGPCR-x. The nGPCR-x also may be expressed in-frame with a tag sequence (e.g., polyhistidine, hemagglutinin, FLAG) to facilitate purification. Moreover, it will be appreciated that many of the uses for nGPCR-x polypeptides, such as assays described below, do not require purification of nGPCR-x from the host cell.

10 *Expression of nGPCR-x in 293 cells*

For expression of nGPCR-x in mammalian cells HEK293 (transformed human, primary embryonic kidney cells), a plasmid bearing the relevant nGPCR-x coding sequence is prepared, using vector pSecTag2A (Invitrogen). Vector pSecTag2A contains the murine IgK chain leader sequence for secretion, the c-myc epitope for detection of the recombinant protein with the anti-myc antibody, a C-terminal polyhistidine for purification with nickel chelate chromatography, and a Zeocin resistant gene for selection of stable transfectants. The forward primer for amplification of this GPCR cDNA is determined by routine procedures and preferably contains a 5' extension of nucleotides to introduce the *HindIII* cloning site and nucleotides matching the GPCR sequence. The reverse primer is also determined by routine procedures and preferably contains a 5' extension of nucleotides to introduce an *XhoI* restriction site for cloning and nucleotides corresponding to the reverse complement of the nGPCR-x sequence. The PCR conditions are 55C as the annealing temperature. The PCR product is gel purified and cloned into the *HindIII-XhoI* sites of the vector.

The DNA is purified using Qiagen chromatography columns and transfected into 293 cells using DOTAP™ transfection media (Boehringer Mannheim, Indianapolis, IN). Transiently transfected cells are tested for expression after 24 hours of transfection, using western blots probed with anti-His and anti-nGPCR-x peptide antibodies. Permanently transfected cells are selected with Zeocin and propagated. Production of the recombinant protein is detected from both cells and media by western blots probed with anti-His, anti-Myc or anti-GPCR peptide antibodies.

30 *Expression of nGPCR-x in COS cells*

For expression of the nGPCR-x in COS7 cells, a polynucleotide molecule having a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:67 can be cloned

into vector p3-CI. This vector is a pUC18-derived plasmid that contains the HCMV (human cytomegalovirus) promoter-intron located upstream from the bGH (bovine growth hormone) polyadenylation sequence and a multiple cloning site. In addition, the plasmid contains the dhfrf (dihydrofolate reductase) gene which provides selection in the presence of the drug
5 methotrexane (MTX) for selection of stable transformants.

The forward primer is determined by routine procedures and preferably contains a 5' extension which introduces an *XbaI* restriction site for cloning, followed by nucleotides which correspond to a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:67. The reverse primer is also determined by routine procedures and preferably contains 5'-
10 extension of nucleotides which introduces a *SalI* cloning site followed by nucleotides which correspond to the reverse complement of a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:67. The PCR consists of an initial denaturation step of 5 minutes at 95C, 30 cycles of 30 seconds denaturation at 95C, 30 seconds annealing at 58C and 30 seconds extension at 72C, followed by 5 minutes extension at 72C. The PCR product is gel purified and
15 ligated into the *XbaI* and *SalI* sites of vector p3-CI. This construct is transformed into *E. coli* cells for amplification and DNA purification. The DNA is purified with Qiagen chromatography columns and transfected into COS 7 cells using Lipofectamine™ reagent from BRL, following the manufacturer's protocols. Forty-eight and 72 hours after transfection, the media and the cells are tested for recombinant protein expression.

20 nGPCR-x expressed from a COS cell culture can be purified by concentrating the cell-growth media to about 10 mg of protein/ml, and purifying the protein by, for example, chromatography. Purified nGPCR-x is concentrated to 0.5 mg/ml in an Amicon concentrator fitted with a YM-10 membrane and stored at -80C.

Expression of nGPCR-x in Insect Cells

25 For expression of nGPCR-x in a baculovirus system, a polynucleotide molecule having a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:67 can be amplified by PCR. The forward primer is determined by routine procedures and preferably contains a 5' extension which adds the *NdeI* cloning site, followed by nucleotides which correspond to a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID
30 NO:67. The reverse primer is also determined by routine procedures and preferably contains a 5' extension which introduces the *KpnI* cloning site, followed by nucleotides which correspond to the reverse complement of a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:67.

The PCR product is gel purified, digested with *NdeI* and *KpnI*, and cloned into the corresponding sites of vector pACHTL-A (Pharmingen, San Diego, CA). The pACHTL expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV), and a 6XHis tag upstream from the multiple cloning site. A protein kinase site for phosphorylation and a thrombin site for excision of the recombinant protein precede the multiple cloning site is also present. Of course, many other baculovirus vectors could be used in place of pACHTL-A, such as pAc373, pVL941 and pAcIM1. Other suitable vectors for the expression of GPCR polypeptides can be used, provided that the vector construct includes appropriately located signals for transcription, translation, and trafficking, such as an in-frame AUG and a signal peptide, as required. Such vectors are described in Luckow *et al.*, Virology 170:31-39, among others. The virus is grown and isolated using standard baculovirus expression methods, such as those described in Summers *et al.* (A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures, Texas Agricultural Experimental Station Bulletin No. 1555 (1987)).

In a preferred embodiment, pACHTL-A containing nGPCR-x gene is introduced into baculovirus using the "BaculoGold™" transfection kit (Pharmingen, San Diego, CA) using methods established by the manufacturer. Individual virus isolates are analyzed for protein production by radiolabeling infected cells with ³⁵S-methionine at 24 hours post infection. Infected cells are harvested at 48 hours post infection, and the labeled proteins are visualized by SDS-PAGE. Viruses exhibiting high expression levels can be isolated and used for scaled up expression.

For expression of a nGPCR-x polypeptide in a Sf9 cells, a polynucleotide molecule having a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:67 can be amplified by PCR using the primers and methods described above for baculovirus expression.

The nGPCR-x cDNA is cloned into vector pACHTL-A (Pharmingen) for expression in Sf9 insect. The insert is cloned into the *NdeI* and *KpnI* sites, after elimination of an internal *NdeI* site (using the same primers described above for expression in baculovirus). DNA is purified with Qiagen chromatography columns and expressed in Sf9 cells. Preliminary Western blot experiments from non-purified plaques are tested for the presence of the recombinant protein of the expected size which reacted with the GPCR-specific antibody. These results are confirmed after further purification and expression optimization in HiG5 cells.

Example 8: Interaction Trap/Two-Hybrid System

In order to assay for nGPCR-x-interacting proteins, the interaction trap/two-hybrid library screening method can be used. This assay was first described in Fields *et al.*, *Nature*, 1989, 340, 245, which is incorporated herein by reference in its entirety. A protocol is published in Current Protocols in Molecular Biology 1999, John Wiley & Sons, NY, and Ausubel, F. M. *et al.* 1992, Short protocols in molecular biology, Fourth edition, Greene and Wiley-interscience, NY, each of which is incorporated herein by reference in its entirety. Kits are available from Clontech, Palo Alto, CA (Matchmaker Two-Hybrid System 3).

A fusion of the nucleotide sequences encoding all or partial nGPCR-x and the yeast transcription factor GAL4 DNA-binding domain (DNA-BD) is constructed in an appropriate plasmid (*i.e.*, pGBKT7) using standard subcloning techniques. Similarly, a GAL4 active domain (AD) fusion library is constructed in a second plasmid (*i.e.*, pGADT7) from cDNA of potential GPCR-binding proteins (for protocols on forming cDNA libraries, see Sambrook *et al.* 1989, Molecular cloning: a laboratory manual, second edition, Cold Spring Harbor Press, Cold Spring Harbor, NY), which is incorporated herein by reference in its entirety. The DNA-BD/nGPCR-x fusion construct is verified by sequencing, and tested for autonomous reporter gene activation and cell toxicity, both of which would prevent a successful two-hybrid analysis. Similar controls are performed with the AD/library fusion construct to ensure expression in host cells and lack of transcriptional activity. Yeast cells are transformed (*ca.* 10⁵ transformants/mg DNA) with both the nGPCR-x and library fusion plasmids according to standard procedures (Ausubel *et al.*, 1992, Short protocols in molecular biology, fourth edition, Greene and Wiley-interscience, NY, which is incorporated herein by reference in its entirety). *In vivo* binding of DNA-BD/nGPCR-x with AD/library proteins results in transcription of specific yeast plasmid reporter genes (*i.e.*, lacZ, HIS3, ADE2, LEU2). Yeast cells are plated on nutrient-deficient media to screen for expression of reporter genes. Colonies are dually assayed for β -galactosidase activity upon growth in Xgal (5-bromo-4-chloro-3-indolyl- β -D-galactoside) supplemented media (filter assay for β -galactosidase activity is described in Breeden *et al.*, Cold Spring Harb. Symp. Quant. Biol., 1985, 50, 643, which is incorporated herein by reference in its entirety). Positive AD-library plasmids are rescued from transformants and reintroduced into the original yeast strain as well as other strains containing unrelated DNA-BD fusion proteins to confirm specific nGPCR-x/library protein interactions. Insert DNA is sequenced to verify the presence of an open reading frame fused to GAL4 AD and to determine the identity of the nGPCR-x-binding protein.

Example 9: Mobility Shift DNA-Binding Assay Using Gel Electrophoresis

A gel electrophoresis mobility shift assay can rapidly detect specific protein-DNA interactions. Protocols are widely available in such manuals as Sambrook *et al.* 1989, *Molecular cloning: a laboratory manual*, second edition, Cold Spring Harbor Press, Cold Spring Harbor, NY and Ausubel, F. M. *et al.*, 1992, *Short Protocols in Molecular Biology*, fourth edition, Greene and Wiley-interscience, NY, each of which is incorporated herein by reference in its entirety.

Probe DNA(<300 bp) is obtained from synthetic oligonucleotides, restriction endonuclease fragments, or PCR fragments and end-labeled with ^{32}P . An aliquot of purified nGPCR-x (*ca.* 15 μg) or crude nGPCR-x extract (*ca.* 15 ng) is incubated at constant temperature (in the range 22-37C) for at least 30 minutes in 10-15 μl of buffer (*i.e.* TAE or TBE, pH 8.0-8.5) containing radiolabeled probe DNA, nonspecific carrier DNA (*ca.* 1 μg), BSA (300 $\mu\text{g}/\text{ml}$), and 10% (v/v) glycerol. The reaction mixture is then loaded onto a polyacrylamide gel and run at 30-35 mA until good separation of free probe DNA from protein-DNA complexes occurs. The gel is then dried and bands corresponding to free DNA and protein-DNA complexes are detected by autoradiography.

Example 10: Antibodies to nGPCR-x

Standard techniques are employed to generate polyclonal or monoclonal antibodies to the nGPCR-x receptor, and to generate useful antigen-binding fragments thereof or variants thereof, including "humanized" variants. Such protocols can be found, for example, in Sambrook *et al.* (1989) and Harlow *et al.* (Eds.), *Antibodies A Laboratory Manual*; Cold Spring Harbor Laboratory; Cold Spring Harbor, NY (1988). In one embodiment, recombinant nGPCR-x polypeptides (or cells or cell membranes containing such polypeptides) are used as antigen to generate the antibodies. In another embodiment, one or more peptides having amino acid sequences corresponding to an immunogenic portion of nGPCR-x (*e.g.*, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more amino acids) are used as antigen. Peptides corresponding to extracellular portions of nGPCR-x, especially hydrophilic extracellular portions, are preferred. The antigen may be mixed with an adjuvant or linked to a hapten to increase antibody production.

Polyclonal or Monoclonal antibodies

As one exemplary protocol, recombinant nGPCR-x or a synthetic fragment thereof is used to immunize a mouse for generation of monoclonal antibodies (or larger mammal, such as a rabbit, for polyclonal antibodies). To increase antigenicity, peptides are conjugated to Keyhole

Lympet Hemocyanin (Pierce), according to the manufacturer's recommendations. For an initial injection, the antigen is emulsified with Freund's Complete Adjuvant and injected subcutaneously. At intervals of two to three weeks, additional aliquots of nGPCR-x antigen are emulsified with Freund's Incomplete Adjuvant and injected subcutaneously. Prior to the final booster injection, a serum sample is taken from the immunized mice and assayed by western blot to confirm the presence of antibodies that immunoreact with nGPCR-x. Serum from the immunized animals may be used as polyclonal antisera or used to isolate polyclonal antibodies that recognize nGPCR-x. Alternatively, the mice are sacrificed and their spleen removed for generation of monoclonal antibodies.

To generate monoclonal antibodies, the spleens are placed in 10 ml serum-free RPMI 1640, and single cell suspensions are formed by grinding the spleens in serum-free RPMI 1640, supplemented with 2 mM L-glutamine, 1 mM sodium pyruvate, 100 units/ml penicillin, and 100 µg/ml streptomycin (RPMI) (Gibco, Canada). The cell suspensions are filtered and washed by centrifugation and resuspended in serum-free RPMI. Thymocytes taken from three naive Balb/c mice are prepared in a similar manner and used as a Feeder Layer. NS-1 myeloma cells, kept in log phase in RPMI with 10% fetal bovine serum (FBS) (Hyclone Laboratories, Inc., Logan, Utah) for three days prior to fusion, are centrifuged and washed as well.

To produce hybridoma fusions, spleen cells from the immunized mice are combined with NS-1 cells and centrifuged, and the supernatant is aspirated. The cell pellet is dislodged by tapping the tube, and 2 ml of 37C PEG 1500 (50% in 75 mM HEPES, pH 8.0) (Boehringer-Mannheim) is stirred into the pellet, followed by the addition of serum-free RPMI. Thereafter, the cells are centrifuged, resuspended in RPMI containing 15% FBS, 100 µM sodium hypoxanthine, 0.4 µM aminopterin, 16 µM thymidine (HAT) (Gibco), 25 units/ml IL-6 (Boehringer-Mannheim) and 1.5×10^6 thymocytes/ml, and plated into 10 Corning flat-bottom 96-well tissue culture plates (Corning, Corning New York).

On days 2, 4, and 6 after the fusion, 100 µl of medium is removed from the wells of the fusion plates and replaced with fresh medium. On day 8, the fusions are screened by ELISA, testing for the presence of mouse IgG that binds to nGPCR-x. Selected fusion wells are further cloned by dilution until monoclonal cultures producing anti-nGPCR-x antibodies are obtained.

Humanization of anti-nGPCR-x monoclonal antibodies

The expression pattern of nGPCR-x as reported herein and the proven track record of GPCRs as targets for therapeutic intervention suggest therapeutic indications for nGPCR-x inhibitors (antagonists). nGPCR-x-neutralizing antibodies comprise one class of therapeutics

useful as nGPCR-x antagonists. Following are protocols to improve the utility of anti-nGPCR-x monoclonal antibodies as therapeutics in humans by "humanizing" the monoclonal antibodies to improve their serum half-life and render them less immunogenic in human hosts (*i.e.*, to prevent human antibody response to non-human anti-nGPCR-x antibodies).

5 The principles of humanization have been described in the literature and are facilitated by the modular arrangement of antibody proteins. To minimize the possibility of binding complement, a humanized antibody of the IgG4 isotype is preferred.

For example, a level of humanization is achieved by generating chimeric antibodies comprising the variable domains of non-human antibody proteins of interest with the constant
10 domains of human antibody molecules. (See, *e.g.*, Morrison *et al.*, Adv. Immunol., 44:65-92 (1989)). The variable domains of nGPCR-x-neutralizing anti-nGPCR-x antibodies are cloned from the genomic DNA of a B-cell hybridoma or from cDNA generated from mRNA isolated from the hybridoma of interest. The V region gene fragments are linked to exons encoding human antibody constant domains, and the resultant construct is expressed in suitable
15 mammalian host cells (*e.g.*, myeloma or CHO cells).

To achieve an even greater level of humanization, only those portions of the variable region gene fragments that encode antigen-binding complementarity determining regions ("CDR") of the non-human monoclonal antibody genes are cloned into human antibody sequences. (See, *e.g.*, Jones *et al.*, Nature 321:522-525 (1986); Riechmann *et al.*, Nature
20 332:323-327 (1988); Verhoeyen *et al.*, Science 239:1534-36 (1988); and Tempest *et al.*, Bio/Technology 9: 266-71 (1991)). If necessary, the β -sheet framework of the human antibody surrounding the CDR3 regions also is modified to more closely mirror the three dimensional structure of the antigen-binding domain of the original monoclonal antibody. (See Kettleborough *et al.*, Protein Engin., 4:773-783 (1991); and Foote *et al.*, J. Mol. Biol.,
25 224:487-499 (1992)).

In an alternative approach, the surface of a non-human monoclonal antibody of interest is humanized by altering selected surface residues of the non-human antibody, *e.g.*, by site-directed mutagenesis, while retaining all of the interior and contacting residues of the non-human antibody. See Padlan, Molecular Immunol., 28(4/5):489-98 (1991).

30 The foregoing approaches are employed using nGPCR-x-neutralizing anti-nGPCR-x monoclonal antibodies and the hybridomas that produce them to generate humanized nGPCR-x-neutralizing antibodies useful as therapeutics to treat or palliate conditions wherein nGPCR-x expression or ligand-mediated nGPCR-x signaling is detrimental.

Human nGPCR-x-Neutralizing Antibodies from Phage Display

Human nGPCR-x-neutralizing antibodies are generated by phage display techniques such as those described in Aujame *et al.*, Human Antibodies 8(4):155-168 (1997); Hoogenboom, TIBTECH 15:62-70 (1997); and Rader *et al.*, Curr. Opin. Biotechnol. 8:503-508 (1997), each of which is incorporated herein by reference in its entirety. For example, antibody variable regions in the form of Fab fragments or linked single chain Fv fragments are fused to the amino terminus of filamentous phage minor coat protein pIII. Expression of the fusion protein and incorporation thereof into the mature phage coat results in phage particles that present an antibody on their surface and contain the genetic material encoding the antibody. A phage library comprising such constructs is expressed in bacteria, and the library is screened for nGPCR-x-specific phage-antibodies using labeled or immobilized nGPCR-x as antigen-probe.

Human nGPCR-x-neutralizing antibodies from transgenic mice

Human nGPCR-x-neutralizing antibodies are generated in transgenic mice essentially as described in Bruggemann *et al.*, Immunol. Today 17(8):391-97 (1996) and Bruggemann *et al.*, Curr. Opin. Biotechnol. 8:455-58 (1997). Transgenic mice carrying human V-gene segments in germline configuration and that express these transgenes in their lymphoid tissue are immunized with a nGPCR-x composition using conventional immunization protocols. Hybridomas are generated using B cells from the immunized mice using conventional protocols and screened to identify hybridomas secreting anti-nGPCR-x human antibodies (*e.g.*, as described above).

Example 11: Assays to Identify Modulators of nGPCR-x Activity

Set forth below are several nonlimiting assays for identifying modulators (agonists and antagonists) of nGPCR-x activity. Among the modulators that can be identified by these assays are natural ligand compounds of the receptor; synthetic analogs and derivatives of natural ligands; antibodies, antibody fragments, and/or antibody-like compounds derived from natural antibodies or from antibody-like combinatorial libraries; and/or synthetic compounds identified by high-throughput screening of libraries; and the like. All modulators that bind nGPCR-x are useful for identifying nGPCR-x in tissue samples (*e.g.*, for diagnostic purposes, pathological purposes, and the like). Agonist and antagonist modulators are useful for up-regulating and down-regulating nGPCR-x activity, respectively, to treat disease states characterized by abnormal levels of nGPCR-x activity. The assays may be performed using single putative modulators, and/or may be performed using a known agonist in combination with candidate antagonists (or *visa versa*).

A. cAMP Assays

In one type of assay, levels of cyclic adenosine monophosphate (cAMP) are measured in nGPCR-x-transfected cells that have been exposed to candidate modulator compounds.

Protocols for cAMP assays have been described in the literature. (See, *e.g.*, Sutherland *et al.*, *Circulation* 37: 279 (1968); Frandsen *et al.*, *Life Sciences* 18: 529-541 (1976); Dooley *et al.*, *Journal of Pharmacology and Experimental Therapeutics* 283 (2): 735-41 (1997); and George *et al.*, *Journal of Biomolecular Screening* 2 (4): 235-40 (1997)). An exemplary protocol for such an assay, using an Adenylyl Cyclase Activation FlashPlate® Assay from NEN™ Life Science Products, is set forth below.

Briefly, the nGPCR-x coding sequence (*e.g.*, a cDNA or intronless genomic DNA) is subcloned into a commercial expression vector, such as pzeoSV2 (Invitrogen), and transiently transfected into Chinese Hamster Ovary (CHO) cells using known methods, such as the transfection protocol provided by Boehringer-Mannheim when supplying the FuGENE 6 transfection reagent. Transfected CHO cells are seeded into 96-well microplates from the FlashPlate® assay kit, which are coated with solid scintillant to which antisera to cAMP has been bound. For a control, some wells are seeded with wild type (untransfected) CHO cells. Other wells in the plate receive various amounts of a cAMP standard solution for use in creating a standard curve.

One or more test compounds (*i.e.*, candidate modulators) are added to the cells in each well, with water and/or compound-free medium/diluent serving as a control or controls. After treatment, cAMP is allowed to accumulate in the cells for exactly 15 minutes at room temperature. The assay is terminated by the addition of lysis buffer containing [¹²⁵I]-labeled cAMP, and the plate is counted using a Packard Topcount™ 96-well microplate scintillation counter. Unlabeled cAMP from the lysed cells (or from standards) and fixed amounts of [¹²⁵I]-cAMP compete for antibody bound to the plate. A standard curve is constructed, and cAMP values for the unknowns are obtained by interpolation. Changes in intracellular cAMP levels of cells in response to exposure to a test compound are indicative of nGPCR-x modulating activity. Modulators that act as agonists of receptors which couple to the G_s subtype of G proteins will stimulate production of cAMP, leading to a measurable 3-10 fold increase in cAMP levels. Agonists of receptors which couple to the G_{i/o} subtype of G proteins will inhibit forskolin-stimulated cAMP production, leading to a measurable decrease in cAMP levels of 50-100%. Modulators that act as inverse agonists will reverse these effects at receptors that are either constitutively active or activated by known agonists.

B. *Aequorin Assays*

In another assay, cells (e.g., CHO cells) are transiently co-transfected with both a nGPCR-x expression construct and a construct that encodes the photoprotein apoaequorin. In the presence of the cofactor coelenterazine, apoaequorin will emit a measurable luminescence that is proportional to the amount of intracellular (cytoplasmic) free calcium. (See generally, Cobbold, et al. "Aequorin measurements of cytoplasmic free calcium," In: McCormack J.G. and Cobbold P.H., eds., *Cellular Calcium: A Practical Approach*. Oxford:IRL Press (1991); Stables et al., *Analytical Biochemistry* 252: 115-26 (1997); and Haugland, *Handbook of Fluorescent Probes and Research Chemicals*, Sixth edition. Eugene OR: Molecular Probes (1996).)

In one exemplary assay, nGPCR-x is subcloned into the commercial expression vector pzeoSV2 (Invitrogen) and transiently co-transfected along with a construct that encodes the photoprotein apoaequorin (Molecular Probes, Eugene, OR) into CHO cells using the transfection reagent FuGENE 6 (Boehringer-Mannheim) and the transfection protocol provided in the product insert.

The cells are cultured for 24 hours at 37C in MEM (Gibco/BRL, Gaithersburg, MD) supplemented with 10% fetal bovine serum, 2 mM glutamine, 10 U/ml penicillin and 10 µg/ml streptomycin, at which time the medium is changed to serum-free MEM containing 5 µM coelenterazine (Molecular Probes, Eugene, OR). Culturing is then continued for two additional hours at 37C. Subsequently, cells are detached from the plate using VERSEN (Gibco/BRL), washed, and resuspended at 200,000 cells/ml in serum-free MEM.

Dilutions of candidate nGPCR-x modulator compounds are prepared in serum-free MEM and dispensed into wells of an opaque 96-well assay plate at 50 µl/well. Plates are then loaded onto an MLX microtiter plate luminometer (Dynex Technologies, Inc., Chantilly, VA). The instrument is programmed to dispense 50 µl cell suspensions into each well, one well at a time, and immediately read luminescence for 15 seconds. Dose-response curves for the candidate modulators are constructed using the area under the curve for each light signal peak. Data are analyzed with SlideWrite, using the equation for a one-site ligand, and EC₅₀ values are obtained. Changes in luminescence caused by the compounds are considered indicative of modulatory activity. Modulators that act as agonists at receptors which couple to the G_q subtype of G proteins give an increase in luminescence of up to 100 fold. Modulators that act as inverse agonists will reverse this effect at receptors that are either constitutively active or activated by known agonists.

C. *Luciferase Reporter Gene Assay*

The photoprotein luciferase provides another useful tool for assaying for modulators of nGPCR-x activity. Cells (e.g., CHO cells or COS 7 cells) are transiently co-transfected with both a nGPCR-x expression construct (e.g., nGPCR-x in pzeoSV2) and a reporter construct
5 which includes a gene for the luciferase protein downstream from a transcription factor binding site, such as the cAMP-response element (CRE), AP-1, or NF-kappa B. Agonist binding to receptors coupled to the G_s subtype of G proteins leads to increases in cAMP, thereby activating the CRE transcription factor and resulting in expression of the luciferase gene. Agonist binding to receptors coupled to the G_q subtype of G protein leads to production of diacylglycerol that
10 activates protein kinase C, which activates the AP-1 or NF-kappa B transcription factors, in turn resulting in expression of the luciferase gene. Expression levels of luciferase reflect the activation status of the signaling events. (See generally, George *et al.*, *Journal of Biomolecular Screening*, 2(4): 235-240 (1997); and Stratowa *et al.*, *Current Opinion in Biotechnology* 6: 574-581 (1995)). Luciferase activity may be quantitatively measured using, e.g., luciferase
15 assay reagents that are commercially available from Promega (Madison, WI).

In one exemplary assay, CHO cells are plated in 24-well culture dishes at a density of 100,000 cells/well one day prior to transfection and cultured at 37C in MEM (Gibco/BRL) supplemented with 10% fetal bovine serum, 2 mM glutamine, 10 U/ml penicillin and 10 µg/ml streptomycin. Cells are transiently co-transfected with both a nGPCR-x expression construct and
20 a reporter construct containing the luciferase gene. The reporter plasmids CRE-luciferase, AP-1-luciferase and NF-kappaB-luciferase may be purchased from Stratagene (LaJolla, CA). Transfections are performed using the FuGENE 6 transfection reagent (Boehringer-Mannheim) according to the supplier's instructions. Cells transfected with the reporter construct alone are used as a control. Twenty-four hours after transfection, cells are washed once with PBS
25 pre-warmed to 37C. Serum-free MEM is then added to the cells either alone (control) or with one or more candidate modulators and the cells are incubated at 37C for five hours. Thereafter, cells are washed once with ice-cold PBS and lysed by the addition of 100 µl of lysis buffer per well from the luciferase assay kit supplied by Promega. After incubation for 15 minutes at room temperature, 15 µl of the lysate is mixed with 50 µl of substrate solution (Promega) in an
30 opaque-white, 96-well plate, and the luminescence is read immediately on a Wallace model 1450 MicroBeta scintillation and luminescence counter (Wallace Instruments, Gaithersburg, MD).

Differences in luminescence in the presence versus the absence of a candidate modulator compound are indicative of modulatory activity. Receptors that are either constitutively active or activated by agonists typically give a 3 to 20-fold stimulation of luminescence compared to cells transfected with the reporter gene alone. Modulators that act as inverse agonists will reverse
5 this effect.

D. Intracellular calcium measurement using FLIPR

Changes in intracellular calcium levels are another recognized indicator of G protein-coupled receptor activity, and such assays can be employed to screen for modulators of nGPCR-x activity. For example, CHO cells stably transfected with a nGPCR-x expression vector are
10 plated at a density of 4×10^4 cells/well in Packard black-walled, 96-well plates specially designed to discriminate fluorescence signals emanating from the various wells on the plate. The cells are incubated for 60 minutes at 37C in modified Dulbecco's PBS (D-PBS) containing 36 mg/L pyruvate and 1 g/L glucose with the addition of 1% fetal bovine serum and one of four calcium indicator dyes (Fluo-3TM AM, Fluo-4TM AM, Calcium GreenTM-1 AM, or Oregon
15 GreenTM 488 BAPTA-1 AM), each at a concentration of 4 μ M. Plates are washed once with modified D-PBS without 1% fetal bovine serum and incubated for 10 minutes at 37C to remove residual dye from the cellular membrane. In addition, a series of washes with modified D-PBS without 1% fetal bovine serum is performed immediately prior to activation of the calcium response.

20 A calcium response is initiated by the addition of one or more candidate receptor agonist compounds, calcium ionophore A23187 (10 μ M; positive control), or ATP (4 μ M; positive control). Fluorescence is measured by Molecular Device's FLIPR with an argon laser (excitation at 488 nm). (See, e.g., Kuntzweiler et al., Drug Development Research, 44(1):14-20 (1998)).

The F-stop for the detector camera was set at 2.5 and the length of exposure was

25 0.4 milliseconds. Basal fluorescence of cells was measured for 20 seconds prior to addition of candidate agonist, ATP, or A23187, and the basal fluorescence level was subtracted from the response signal. The calcium signal is measured for approximately 200 seconds, taking readings every two seconds. Calcium ionophore A23187 and ATP increase the calcium signal 200% above baseline levels. In general, activated GPCRs increase the calcium signal approximately
30 10-15% above baseline signal.

E. Mitogenesis Assay

In a mitogenesis assay, the ability of candidate modulators to induce or inhibit nGPCR-x-mediated cell division is determined. (See, e.g., Lajiness et al., Journal of Pharmacology and

Experimental Therapeutics 267(3): 1573-1581 (1993)). For example, CHO cells stably expressing nGPCR-x are seeded into 96-well plates at a density of 5000 cells/well and grown at 37C in MEM with 10% fetal calf serum for 48 hours, at which time the cells are rinsed twice with serum-free MEM. After rinsing, 80 µl of fresh MEM, or MEM containing a known mitogen, is added along with 20 µl MEM containing varying concentrations of one or more candidate modulators or test compounds diluted in serum-free medium. As controls, some wells on each plate receive serum-free medium alone, and some receive medium containing 10% fetal bovine serum. Untransfected cells or cells transfected with vector alone also may serve as controls.

After culture for 16-18 hours, 1 µCi of [³H]-thymidine (2 Ci/mmol) is added to the wells and cells are incubated for an additional 2 hours at 37C. The cells are trypsinized and collected on filter mats with a cell harvester (Tomtec); the filters are then counted in a Betaplate counter. The incorporation of [³H]-thymidine in serum-free test wells is compared to the results achieved in cells stimulated with serum (positive control). Use of multiple concentrations of test compounds permits creation and analysis of dose-response curves using the non-linear, least squares fit equation: $A = B \times [C / (D + C)] + G$ where A is the percent of serum stimulation; B is the maximal effect minus baseline; C is the EC₅₀; D is the concentration of the compound; and G is the maximal effect. Parameters B, C and G are determined by Simplex optimization.

Agonists that bind to the receptor are expected to increase [³H]-thymidine incorporation into cells, showing up to 80% of the response to serum. Antagonists that bind to the receptor will inhibit the stimulation seen with a known agonist by up to 100%.

F. [³⁵S]GTPγS Binding Assay

Because G protein-coupled receptors signal through intracellular G proteins whose activity involves GTP binding and hydrolysis to yield bound GDP, measurement of binding of the non-hydrolyzable GTP analog [³⁵S]GTPγS in the presence and absence of candidate modulators provides another assay for modulator activity. (See, e.g., Kowal et al., *Neuropharmacology* 37:179-187 (1998).)

In one exemplary assay, cells stably transfected with a nGPCR-x expression vector are grown in 10 cm tissue culture dishes to subconfluence, rinsed once with 5 ml of ice-cold Ca²⁺/Mg²⁺-free phosphate-buffered saline, and scraped into 5 ml of the same buffer. Cells are pelleted by centrifugation (500 x g, 5 minutes), resuspended in TEE buffer (25 mM Tris, pH 7.5, 5 mM EDTA, 5 mM EGTA), and frozen in liquid nitrogen. After thawing, the cells are

homogenized using a Dounce homogenizer (one ml TEE per plate of cells), and centrifuged at 1,000 x g for 5 minutes to remove nuclei and unbroken cells.

The homogenate supernatant is centrifuged at 20,000 x g for 20 minutes to isolate the membrane fraction, and the membrane pellet is washed once with TEE and resuspended in
5 binding buffer (20 mM HEPES, pH 7.5, 150 mM NaCl, 10 mM MgCl₂, 1 mM EDTA). The resuspended membranes can be frozen in liquid nitrogen and stored at -70C until use.

Aliquots of cell membranes prepared as described above and stored at -70C are thawed, homogenized, and diluted into buffer containing 20 mM HEPES, 10 mM MgCl₂, 1 mM EDTA, 120 mM NaCl, 10 μM GDP, and 0.2 mM ascorbate, at a concentration of 10-50 μg/ml. In a final
10 volume of 90 μl, homogenates are incubated with varying concentrations of candidate modulator compounds or 100 μM GTP for 30 minutes at 30C and then placed on ice. To each sample, 10 μl guanosine 5'-O-(3[³⁵S]thio) triphosphate (NEN, 1200 Ci/mmol; [³⁵S]-GTPγS), was added to a final concentration of 100-200 pM. Samples are incubated at 30C for an additional 30 minutes, 1 ml of 10mM HEPES, pH 7.4, 10 mM MgCl₂, at 4C is added and the reaction is stopped by
15 filtration.

Samples are filtered over Whatman GF/B filters and the filters are washed with 20 ml ice-cold 10 mM HEPES, pH 7.4, 10 mM MgCl₂. Filters are counted by liquid scintillation spectroscopy. Nonspecific binding of [³⁵S]-GTPγS is measured in the presence of 100 μM GTP and subtracted from the total. Compounds are selected that modulate the amount of [³⁵S]-GTPγS
20 binding in the cells, compared to untransfected control cells. Activation of receptors by agonists gives up to a five-fold increase in [³⁵S]GTPγS binding. This response is blocked by antagonists.

G. *MAP Kinase Activity Assay*

Evaluation of MAP kinase activity in cells expressing a GPCR provides another assay to identify modulators of GPCR activity. (See, e.g., Lajiness et al., Journal of Pharmacology and
25 Experimental Therapeutics 267(3):1573-1581 (1993) and Boulton et al., Cell 65:663-675 (1991).)

In one embodiment, CHO cells stably transfected with nGPCR-x are seeded into 6-well plates at a density of 70,000 cells/well 48 hours prior to the assay. During this 48-hour period, the cells are cultured at 37C in MEM medium supplemented with 10% fetal bovine serum, 2mM
30 glutamine, 10 U/ml penicillin and 10μg/ml streptomycin. The cells are serum-starved for 1-2 hours prior to the addition of stimulants.

For the assay, the cells are treated with medium alone or medium containing either a candidate agonist or 200 nM Phorbol ester- myristoyl acetate (i.e., PMA, a positive control), and

the cells are incubated at 37C for varying times. To stop the reaction, the plates are placed on ice, the medium is aspirated, and the cells are rinsed with 1 ml of ice-cold PBS containing 1mM EDTA. Thereafter, 200µl of cell lysis buffer (12.5 mM MOPS, pH 7.3, 12.5 mM glycerophosphate, 7.5mM MgCl₂, 0.5mM EGTA, 0.5 mM sodium vanadate, 1mM benzamidine, 1mM dithiothreitol, 10 µg/ml leupeptin, 10 µg/ml aprotinin, 2µg/ml pepstatin A, and 1µM okadaic acid) is added to the cells. The cells are scraped from the plates and homogenized by 10 passages through a 23 3/4 G needle, and the cytosol fraction is prepared by centrifugation at 20,000 x g for 15 minutes.

Aliquots (5-10 µl containing 1-5 µg protein) of cytosol are mixed with 1 mM MAPK Substrate Peptide (APRTPGGRR; SEQ ID NO:137), Upstate Biotechnology, Inc., N.Y.) and 50µM [γ -³²P]ATP (NEN, 3000 Ci/mmol), diluted to a final specific activity of ~2000 cpm/pmol, in a total volume of 25 µl. The samples are incubated for 5 minutes at 30C, and reactions are stopped by spotting 20 µl on 2 cm² squares of Whatman P81 phosphocellulose paper. The filter squares are washed in 4 changes of 1% H₃PO₄, and the squares are subjected to liquid scintillation spectroscopy to quantitate bound label. Equivalent cytosolic extracts are incubated without MAPK substrate peptide, and the bound label from these samples are subtracted from the matched samples with the substrate peptide. The cytosolic extract from each well is used as a separate point. Protein concentrations are determined by a dye binding protein assay (Bio-Rad Laboratories). Agonist activation of the receptor is expected to result in up to a five-fold increase in MAPK enzyme activity. This increase is blocked by antagonists.

H. [³H]Arachidonic Acid Release

The activation of GPCRs also has been observed to potentiate arachidonic acid release in cells, providing yet another useful assay for modulators of GPCR activity. (See, e.g., Kanterman et al., Molecular Pharmacology 39:364-369 (1991).) For example, CHO cells that are stably transfected with a nGPCR-x expression vector are plated in 24-well plates at a density of 15,000 cells/well and grown in MEM medium supplemented with 10% fetal bovine serum, 2 mM glutamine, 10 U/ml penicillin and 10 µg/ml streptomycin for 48 hours at 37C before use. Cells of each well are labeled by incubation with [³H]-arachidonic acid (Amersham Corp., 210 Ci/mmol) at 0.5 µCi/ml in 1 ml MEM supplemented with 10mM HEPES, pH 7.5, and 0.5% fatty-acid-free bovine serum albumin for 2 hours at 37C. The cells are then washed twice with 1 ml of the same buffer.

Candidate modulator compounds are added in 1 ml of the same buffer, either alone or with 10µM ATP and the cells are incubated at 37C for 30 minutes. Buffer alone and mock-

transfected cells are used as controls. Samples (0.5 ml) from each well are counted by liquid scintillation spectroscopy. Agonists which activate the receptor will lead to potentiation of the ATP-stimulated release of [^3H]-arachidonic acid. This potentiation is blocked by antagonists.

I. Extracellular Acidification Rate

5 In yet another assay, the effects of candidate modulators of nGPCR-x activity are assayed by monitoring extracellular changes in pH induced by the test compounds. (See, e.g., Dunlop et al., Journal of Pharmacological and Toxicological Methods 40(1):47-55 (1998).) In one embodiment, CHO cells transfected with a nGPCR-x expression vector are seeded into 12 mm capsule cups (Molecular Devices Corp.) at 4×10^5 cells/cup in MEM supplemented with
10 10% fetal bovine serum, 2 mM L-glutamine, 10 U/ml penicillin, and 10 $\mu\text{g/ml}$ streptomycin. The cells are incubated in this medium at 37C in 5% CO_2 for 24 hours.

Extracellular acidification rates are measured using a Cytosensor microphysiometer (Molecular Devices Corp.). The capsule cups are loaded into the sensor chambers of the microphysiometer and the chambers are perfused with running buffer (bicarbonate-free MEM
15 supplemented with 4 mM L-glutamine, 10 units/ml penicillin, 10 $\mu\text{g/ml}$ streptomycin, 26 mM NaCl) at a flow rate of 100 $\mu\text{l/minute}$. Candidate agonists or other agents are diluted into the running buffer and perfused through a second fluid path. During each 60-second pump cycle, the pump is run for 38 seconds and is off for the remaining 22 seconds. The pH of the running buffer in the sensor chamber is recorded during the cycle from 43-58 seconds, and the pump is
20 re-started at 60 seconds to start the next cycle. The rate of acidification of the running buffer during the recording time is calculated by the Cytosoft program. Changes in the rate of acidification are calculated by subtracting the baseline value (the average of 4 rate measurements immediately before addition of a modulator candidate) from the highest rate measurement obtained after addition of a modulator candidate. The selected instrument detects
25 61 mV/pH unit. Modulators that act as agonists of the receptor result in an increase in the rate of extracellular acidification compared to the rate in the absence of agonist. This response is blocked by modulators which act as antagonists of the receptor.

Example 12: Using nGPCR-x Proteins to Isolate Neurotransmitters

The isolated nGPCR-x proteins can be used to isolate novel or known neurotransmitters
30 (Saito et al., Nature, 400: 265-269, 1999). The cDNAs that encode the isolated nGPCR-x can be cloned into mammalian expression vectors and used to stably or transiently transfect mammalian cells including CHO, Cos or HEK293 cells. Receptor expression can be determined by Northern blot analysis of transfected cells and identification of an appropriately sized mRNA

band (predicted size from the cDNA). Brain regions shown by mRNA analysis to express each of the nGPCR-x proteins could be processed for peptide extraction using any of several protocols ((Reinscheid R.K. et al., Science 270: 243-247, 1996; Sakurai, T., et al., Cell 92: 573-585, 1998; Hinuma, S., et al., Nature 393: 272-276, 1998). Chromatographic fractions of brain
5 extracts could be tested for ability to activate nGPCR-x proteins by measuring second messenger production such as changes in cAMP production in the presence or absence of forskolin, changes in inositol 3-phosphate levels, changes in intracellular calcium levels or by indirect measures of receptor activation including receptor stimulated mitogenesis, receptor mediated changes in extracellular acidification or receptor mediated changes in reporter gene
10 activation in response to cAMP or calcium (these methods should all be referenced in other sections of the patent). Receptor activation could also be monitored by co-transfecting cells with a chimeric $GI_{q/13}$ to force receptor coupling to a calcium stimulating pathway (Conklin et al., Nature 363: 274-276, 1993). Neurotransmitter mediated activation of receptors could also be monitored by measuring changes in [35 S]-GTPKS binding in membrane fractions prepared
15 from transfected mammalian cells. This assay could also be performed using baculoviruses containing nGPCR-x proteins infected into SF9 insect cells.

The neurotransmitter which activates nGPCR-x proteins can be purified to homogeneity through successive rounds of purification using nGPCR-x proteins activation as a measurement of neurotransmitter activity. The composition of the neurotransmitter can be determined by mass
20 spectrometry and Edman degradation if peptidergic. Neurotransmitters isolated in this manner will be bioactive materials which will alter neurotransmission in the central nervous system and will produce behavioral and biochemical changes.

Example 13: Using nGPCR-x Proteins to Isolate and Purify G Proteins

cDNAs encoding nGPCR-x proteins are epitope-tagged at the amino terminus end of
25 the cDNA with the cleavable influenza-hemagglutinin signal sequence followed by the FLAG epitope (IBI, New Haven, CT). Additionally, these sequences are tagged at the carboxyl terminus with DNA encoding six histidine residues. (Amino and Carboxyl Terminal Modifications to Facilitate the Production and Purification of a G Protein-Coupled Receptor, B.K. Kobilka, Analytical Biochemistry, Vol. 231, No. 1, Oct 1995, pp. 269-271). The resulting
30 sequences are cloned into a baculovirus expression vector such as pVL1392 (Invitrogen). The baculovirus expression vectors are used to infect SF-9 insect cells as described (Guan *et al.*, (1992) J. Biol. Chem. 267, 21995-21998). Infected SF-9 cells could be grown in 1000-ml cultures in SF900 II medium (Life Technologies, Inc.) containing 5% fetal calf serum (Gemini,

Calabasas, CA) and 0.1 mg/ml gentamicin (Life Technologies, Inc.) for 48 hours at which time the cells could be harvested. Cell membrane preparations could be separated from soluble proteins following cell lysis. nGPCR-x protein purification is carried out as described for purification of the 92 receptor (Kobilka, Anal. Biochem., 231 (1): 269-271, 1995) including
5 solubilization of the membranes in 0.8-1.0 % n-dodecyl-D-maltoside (DM) (CalBiochem, La Jolla, CA) in buffer containing protease inhibitors followed by Ni-column chromatography using chelating Sepharose™ (Pharmacia, Uppsala, Sweden). The eluate from the Ni-column is further purified on an M1 anti-FLAG antibody column (IBI). Receptor containing fractions are monitored by using receptor specific antibodies following western blot analysis or by SDS-
10 PAGE analysis to look for an appropriate sized protein band (appropriate size would be the predicted molecular weight of the protein). This method of purifying G protein is particularly useful to isolate G proteins that bind to the nGPCR-x proteins in the absence of an activating ligand.

Some of the preferred embodiments of the invention described above are outlined below
15 and include, but are not limited to, the following embodiments. As those skilled in the art will appreciate, numerous changes and modifications may be made to the preferred embodiments of the invention without departing from the spirit of the invention. It is intended that all such variations fall within the scope of the invention. The entire disclosure of each publication cited herein is incorporated herein by reference in its entirety.

What is claimed is:

1. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence homologous to sequences selected from the group consisting of: SEQ ID NO:68 to SEQ ID NO:136, said nucleic acid molecule encoding at
5 least a portion of nGPCR-x.
2. The isolated nucleic acid molecule of claim 1 comprising a sequence that encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO:68 to
10 SEQ ID NO:136.
3. The isolated nucleic acid molecule of claim 1 comprising a sequence homologous to a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:67.
4. The isolated nucleic acid molecule of claim 1 comprising a sequence selected from the
15 group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:67.
5. The isolated nucleic acid molecule of claim 4 comprising a sequence selected from the group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:67.
- 20 6. The isolated nucleic acid molecule of claim 1 wherein said nucleic acid molecule is DNA.
7. The isolated nucleic acid molecule of claim 1 wherein said nucleic acid molecule is RNA.
- 25 8. An expression vector comprising a nucleic acid molecule of any one of claims 1 to 5.
9. The expression vector of claim 8 wherein said nucleic acid molecule comprises a sequence selected from the group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:67.
- 30 10. The expression vector of claim 8 wherein said vector is a plasmid.
11. The expression vector of claim 8 wherein said vector is a viral particle.

12. The expression vector of claim 11 wherein said vector is selected from the group consisting of adenoviruses, baculoviruses, parvoviruses, herpesviruses, poxviruses, adeno-associated viruses, Semliki Forest viruses, vaccinia viruses, and retroviruses.

5

13. The expression vector of claim 8 wherein said nucleic acid molecule is operably connected to a promoter selected from the group consisting of simian virus 40, mouse mammary tumor virus, long terminal repeat of human immunodeficiency virus, maloney virus, cytomegalovirus immediate early promoter, Epstein Barr virus, rous sarcoma virus, human
10 actin, human myosin, human hemoglobin, human muscle creatine, and human metalothionein.

14. A host cell transformed with an expression vector of claim 8.

15. The transformed host cell of claim 14 wherein said cell is a bacterial cell.

15

16. The transformed host cell of claim 15 wherein said bacterial cell is *E. coli*.

17. The transformed host cell of claim 14 wherein said cell is yeast.

20 18. The transformed host cell of claim 17 wherein said yeast is *S. cerevisiae*.

19. The transformed host cell of claim 14 wherein said cell is an insect cell.

20. The transformed host cell of claim 19 wherein said insect cell is *S. frugiperda*.

25

21. The transformed host cell of claim 14 wherein said cell is a mammalian cell.

22. The transformed host cell of claim 21 wherein mammalian cell is selected from the group consisting of chinese hamster ovary cells, HeLa cells, African green monkey kidney cells,
30 human 293 cells, and murine 3T3 fibroblasts.

23. An isolated nucleic acid molecule comprising a nucleotide sequence complementary to at least a portion of a sequence selected from the group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:67, said portion comprising at least 10 nucleotides.

5 24. The nucleic acid molecule of claim 23 wherein said molecule is an antisense oligonucleotide directed to a region of a sequence selected from the group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:67.

10 25. The nucleic acid molecule of claim 24 wherein said oligonucleotide is directed to a regulatory region of a sequence selected from the group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:67.

26. A composition comprising a nucleic acid molecule of any one of claims 1 to 5 or 23 and an acceptable carrier or diluent.

15 27. A composition comprising a recombinant expression vector of claim 8 and an acceptable carrier or diluent.

20 28. A method of producing a polypeptide that comprises a sequence selected from the group of sequences consisting SEQ ID NO:68 to SEQ ID NO:136, and homologs thereof, said method comprising the steps of:

- a) introducing a recombinant expression vector of claim 10 into a compatible host cell;
- b) growing said host cell under conditions for expression of said polypeptide; and
- c) recovering said polypeptide.

25 29. The method of claim 28 wherein said host cell is lysed and said polypeptide is recovered from the lysate of said host cell.

30 30. The method of claim 28 wherein said polypeptide is recovered by purifying the culture medium without lysing said host cell.

31. An isolated polypeptide encoded by a nucleic acid molecule of claim 1.

32. The polypeptide of claim 31 wherein said polypeptide comprises a sequence selected from the group of sequences consisting of SEQ ID NO:68 to SEQ ID NO:136.

33. The polypeptide of claim 31 wherein said polypeptide comprises an amino acid sequence homologous to a sequence selected from the group of sequences consisting of SEQ ID NO:68 to SEQ ID NO:136.

34. The polypeptide of claim 31 wherein said sequence homologous to a sequence selected from the group of sequences consisting of SEQ ID NO:68 to SEQ ID NO:136 comprises at least one conservative amino acid substitution compared to the sequences in the group of sequences consisting of SEQ ID NO:68 to SEQ ID NO:136.

35. The polypeptide of claim 31 wherein said polypeptide comprises an allelic variant of a polypeptide with a sequence selected from the group of sequences consisting of SEQ ID NO:68 to SEQ ID NO:136.

36. A composition comprising a polypeptide of claim 31 and an acceptable carrier or diluent.

37. An isolated antibody which binds to an epitope on a polypeptide of claim 31.

38. The antibody of claim 37 wherein said antibody is a monoclonal antibody.

39. A composition comprising an antibody of claim 37 and an acceptable carrier or diluent.

40. A kit comprising an antibody which binds to a polypeptide of claim 31 and a negative control antibody.

41. The kit of claim 40 further comprising an additional kit component.

42. The kit of claim 41 wherein said additional kit component comprises instructions.

43. The kit comprising a nucleic acid molecule of claim 1 or 2.

44. The kit of claim 43 further comprising an additional kit component.

45. The kit of claim 44 wherein said additional kit component comprises instructions.

5 46. A method of inducing an immune response in a mammal against a polypeptide of claim 31 comprising administering to said mammal an amount of said polypeptide sufficient to induce said immune response.

47. A method for identifying a compound which binds nGPCR-x comprising the steps of:

- 10 a) contacting nGPCR-x with a compound; and
b) determining whether said compound binds nGPCR-x.

48. The method of claim 47 wherein binding of said compound to nGPCR-x is determined by a protein binding assay.

15

49. The method of claim 47 wherein said protein binding assay is selected from the group consisting of a gel-shift assay, Western blot, radiolabeled competition assay, phage-based expression cloning, co-fractionation by chromatography, co-precipitation, cross linking, interaction trap/two-hybrid analysis, southwestern analysis, and ELISA.

20

50. A compound identified by the method of claim 47.

51. A method for identifying a compound which binds a nucleic acid molecule encoding nGPCR-x comprising the steps of:

- 25 a) contacting said nucleic acid molecule encoding nGPCR-x with a compound; and
b) determining whether said compound binds said nucleic acid molecule.

52. The method of claim 51 wherein binding is determined by a gel-shift assay.

30 53. A compound identified by the method of claim 51.

54. A method for identifying a compound which modulates the activity of nGPCR-x comprising the steps of:

- a) contacting nGPCR-x with a compound; and
- b) determining whether nGPCR-x activity has been modulated.

55. The method of claim 54 wherein said activity is neuropeptide binding.

56. The method of claim 54 wherein said activity is neuropeptide signaling.

57. A compound identified by the method of claim 54.

58. A method of identifying an animal homolog of nGPCR-x comprising the steps:

a) comparing the nucleic acid sequences of the animal with a sequence selected from the group of sequence consisting of SEQ ID NO:1 to SEQ ID NO:67, and portions thereof, said portions being at least 10 nucleotides; and

b) identifying nucleic acid sequences of the animal that are homologous to said sequence selected from the group sequence consisting of SEQ ID NO:1 to SEQ ID NO:67, and portions thereof.

59. The method of claim 58 wherein comparing the nucleic acid sequences of the animal with a sequence selected from the group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:67, and portions thereof, said portions being at least 10 nucleotides, is performed by DNA hybridization.

60. The method of claim 58 wherein comparing the nucleic acid sequences of the animal with a sequence selected from the group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:67, and portions thereof, said portions being at least 10 nucleotides, is performed by computer homology search.

61. A method of purifying a G protein from a sample containing said G protein comprising the steps of:

- a) contacting said sample with a polypeptide of claim 1 for a time sufficient to allow said G protein to form a complex with said polypeptide;
- b) isolating said complex from remaining components of said sample;

- c) maintaining said complex under conditions which result in dissociation of said G protein from said polypeptide; and
- d) isolating said G protein from said polypeptide.

5 62. The method of claim 61 wherein said sample comprises an amino acid sequence selected from the group of sequences consisting of SEQ ID NO:68 to SEQ ID NO:136.

63. The method of claim 61 wherein said polypeptide comprises an amino acid sequence homologous to a sequence selected from the group of sequences consisting of SEQ ID NO:68 to
10 SEQ ID NO:136.

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<210> 19
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 <213> Homo sapiens

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 gggcagagat caaccctgag aactgagaa agctgcatga agccaggaac tatgtttgtc 180
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 attaacttca gtaaggtaat tgtgctcaaa ggaagtccca tggcaatgat cacattaaga 360
 atgaaaatcc acatggaata tatgatgtc aaattgcaag agctacctga ttttaagcac 420
 ctgttatgtg ccaagcccag tgctaggtgt ttcaatcctc acaacgcttc aaaatagaag 480

00131PCT1.ST25.txt

tgacttttcc cattttgaag atgagaaaac tgagccccct gaggetcagc tactaataag	540
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atactgtgcc ttctcccaga tttctgtatg gattactgat gtttttttca agcaaataca	660
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cagtgtcaca tatgtatata tgcatata	748

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 <212> DNA
 <213> Homo sapiens

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taacacatgg gattcaaattg gctgtattca gagataaagc agagggccag aaaagcatca	180
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ggaatcttgg ttataagact gtgaaaaata aatatagctc aagacactgt ctgttttagt	660
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<210> 21
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 <212> DNA
 <213> Homo sapiens

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attatgtgtt tgataaaaat aaaaataaaa catatttttg atcactgata tttttatcat	180
aattgaatgt cttataaata attctgccat tagaaaaatt gtataatgtc ctttaattctc	240
cacaatgagt tatattatgt taccactgaa atgaacaaac acaatatagc taagtggcga	300
aatagtgttg ctactacaa tttaaataatc atttaattta acatttatta aaaccaacat	360
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actttatgca actaagaatg ggagggatat gttttttcat acaataaatg ataatcttg	540
tttagtttat aaagaattaa gggcactaaa aactgtgagt ataaaataaa aatcctacag	600

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ccttagttgg ttgcctttct tctcacaaaa tgtttaaagt gatccttgac attttcaaaa 660
 cagagtttga gaagccattt atatgaactt tctattggta aattaactac gtagactcta 720
 tcttaagtaa ttttaattat gtgtagcaca tattt 755

<210> 22
 <211> 602
 <212> DNA
 <213> Homo sapiens

<400> 22
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 accacaaaga gaaccagggt caccagaatg aggatgattc tggaccgtgg ggtcacctca 300
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 aatcttgtct tgcaaagtag aacttgcaat tctggccatg aagaataact agtacctaac 540
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<210> 23
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 <212> DNA
 <213> Homo sapiens

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 gcttccccca gaataagttt ctgtctctaa aacacaagct cttgagcatt tgtttattag 180
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 gcacagagcc ttctgtgtgg ctgtgacagc gaggacaaaa acaatcacat taatgttggt 480
 cgtaggatg gggctttttt gctgtgtgct tttcatggtg gtttttact attcagtcta 540
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<210> 24

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<211> 411
 <212> DNA
 <213> Homo sapiens

<400> 24
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<210> 25
 <211> 411
 <212> DNA
 <213> Homo sapiens

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<210> 26
 <211> 600
 <212> DNA
 <213> Homo sapiens

<400> 26
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 acctgctcaa cactaattag ctctttctca atcctactca cctattcagt atcctttaag 180
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 caaactgctc ctgacttttag caaaaatttt aacaaattta tatgtgtatg aaatatatgt 540
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<210> 27
<211> 681
<212> DNA
<213> Homo sapiens

<400> 27
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tttaaatata ttagctaatt taagcctaata ggcagccttg tcaggtaggt acctttgtcc 660
ccagtttata tacaactgca a 681

<210> 28
<211> 731
<212> DNA
<213> Homo sapiens

<400> 28
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aatgatcctc taacaagctc attttcatac tgataaaatg tgtgtgctag gatttcatac 120
atgctgggtt gaatgggtag gtgataggta cctccaatgt ggactgttag gccagaatg 180
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catatattct agtaccctaa gatactatga cagttgccat gaaggaacct tataaagctc 300
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attcataatt tgcaggataa acaggtcacc agtttaaaaa cagaaaaaaa tccccacaaa 420
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atatttactt atggacacat atttgcctaa attgcattaa gttctataat attactgagt 600
aataattttc ctccctttct gtattgatac agcatctgta aatgcttatc aataggcaaa 660
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tgtgtggcgt a 731

<210> 29
<211> 714

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<212> DNA
 <213> Homo sapiens

<400> 29
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 aacttgattc cattaaattc acccaacagg cctccagagg aagatattac tgctttgata 120
 ttacaaaggg aaaaacagct atggcgtctc tgaaaagcac aacgtgctag gactggaatg 180
 actttaaaac cacacataaa tttctgagag atttttgcc a taaggtacca tccaccttac 240
 tataaaccac atcctaaaat tgtctgcagt gcaaatggat tatgtgcatc caacaggaaa 300
 cagcataggt tgagaagctg ttacttaata gcttcattgt caccacgagt gtaaagtgtg 360
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 tttgaccaac tcaactgtggc tcagggtccc ttacgcagcc tgttggggaa accagtgggt 480
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 gaggtccttt catcactatt gccactagtc cttccgactt cctgtgccct gtttcttctt 660
 ttattggaac ccaagaacga gtaaacaatag cattttcaaa catcccgccc cctt 714

<210> 30
 <211> 655
 <212> DNA
 <213> Homo sapiens

<400> 30
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 aaagaatggg aaatagatga ctagacactt cagagatgat caacccaaaa tggtaaacad 120
 tccacatgaa aaacatttta aatttactaa gtcaaggaaa tcacaattaa agtgattaag 180
 agctatcata ttagtctggt ccaatataaa atagtaacac atttaatat ggcagatatg 240
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 ttctctaaaa tgtatttatg aaaccaactt gattgcatat actaaatttt tcagttcaaa 600
 tatctgataa gagatgtccc cagggttttt taataacgta taccttgtaa tcata 655

<210> 31
 <211> 607
 <212> DNA
 <213> Homo sapiens

<400> 31
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 aagtatttac agatgtgagt atatacatgg aattagtata cacacatatt tctttgctct 120

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 tctgctt 607

<210> 32
 <211> 613
 <212> DNA
 <213> Homo sapiens

<400> 32
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 aacacactcc cggctggggt gtgagtgcct gagaaccaca aacgtacctc cgtcctgcct 180
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 ctccatttca tctctgcccc caaataaaga aaaaaaaaaa gtctctctga cttattttct 600
 agctccaggt caa 613

<210> 33
 <211> 681
 <212> DNA
 <213> Homo sapiens

<400> 33
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gctaaaccaa aatacaatac tgcaataaaa aattgtatgt atgatatgat cacacttatt	600
ggaatttatg taaaattata tgcaagtata tgtatgtgta aatatttttag aagaaaaaaa	660
ttacaaacag aacaagaaaa g	681

<210> 34
 <211> 632
 <212> DNA
 <213> Homo sapiens

<400> 34	
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gggaccaatc tcagaaacac tgggatacaa ga	632

<210> 35
 <211> 706
 <212> DNA
 <213> Homo sapiens

<400> 35	
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tggagtctcg gcggctcctc cgaacacagc aatcgggtgag tgagtgggac tgagaggccc	180
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gtcaccgaca ggacgctcat gagatcatcc acagaccagg aagccacaag catggacaca	600

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gcaaaagtca tgagacatgt caagcaaaaa agatagatat ttcagg 706

<210> 36
<211> 682
<212> DNA
<213> Homo sapiens

<400> 36
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gacaaactac aagatacttt aagctgcaaa gtcaacacga gacttctggc ccaaattgtg 240
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aaactaaacc taaagcaagc ag 682

<210> 37
<211> 539
<212> DNA
<213> Homo sapiens

<400> 37
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ccacaaggga tgaaatagac agtgagacag tgagcccact tgaggacctc gtccagtgtt 480
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<210> 38
<211> 682
<212> DNA
<213> Homo sapiens

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<400> 38
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tggagatgaa ggcttctctc ctttcaccca gtacctcact tgccgcaaaa ctgaaagaaa 180
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<213> Homo sapiens

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<212> DNA
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<210> 47
<211> 429
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<213> Homo sapiens

<400> 47
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<212> DNA
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<212> DNA
<213> Homo sapiens

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<213> Homo sapiens

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<210> 51
<211> 556
<212> DNA
<213> Homo sapiens

<400> 51
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 <212> DNA
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<210> 55
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 <212> DNA
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<400> 55
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 <212> DNA
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 <213> Homo sapiens

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ccttttactc atgcctctct gctggagttc catattcctg attttctcac tgttgccctt 180
catgaccatg aaacctttgt tcacccatcc attcccattt ctttcaagta ctctttgaag 240
tttattaaag ccacttctct cacagtcgtt ttagattttc ccttaagtag cctctaaatc 300
tgcaagtccc tgaccttggg cattctgggt actctaaagt ggtgcctgta gataacagat 360
attccaatga ctatatctag cttaatgatt ctcaaattat tcacatgggc agtcagtatc 420
atgaggtcct tggggagtca tcatgaagat gactaaaaat tcaaataaat ggtgagagtc 480
ac 482

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<210> 60
 <211> 609
 <212> DNA
 <213> Homo sapiens

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<400> 60
acttcttcat gtctttggca actttgttta atttttttaa agttgctagt ctctttttct 60
taatgaacgg tccttgtttc atgttcgtgg ccattttcat ggtcagccgt ctgggcaagc 120
tgctttttct cttcttgtgg taccactcct cctctcctta ctgctcagct gtagtttcac 180
acaacaagct aagtggagct cgtgggggtca cttacaggaa acaaggagca tgactcgcac 240
ccatgaagtt agaaatggca cacggggagg ggagatagag cagatccgtg cacagcactc 300
atgtgtaaaa tatgcctgca ccactgtctg ctttgcgttt gagttcaaaa caaaaggctt 360
ccgtgaaata taataagcta tatatatattt tcagagtgac aagaattgtc tcgcttcctt 420
tcagttccca gacttctcca aagttagtct aatgtcatga cattgcctgg ggaggccaga 480
ggctggcctc agagacgaga aagcaggtag cttggcttgg gcttgtttct taagggtcta 540
ggtgcctaca gcgtagaaat tcagcatttg cagagcaccc gaggtgaggg gctgggggac 600
ggcagagcc 609

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<210> 61
 <211> 568
 <212> DNA
 <213> Homo sapiens

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<400> 61
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tcaagtttca aatttagtta caccatttaa aatgcatttt ccatggcttt gttttttttc 120
tcacttttaa tttcattttg cttcagttga gtactttcca ttgggtctatc cgtcagtgtc 180
cctgtttcct caattgtgtt gatttgagag tcaactcaa ggcatttttt atccttttta 240
ctgtgtttac atttatatca tattcatgtc cttcttatta tcctcgagtc tcagctgata 300
gtagtcattt ctttatgcat gttgttcac ttactgtaa catttaacac aaaaattata 360
tctatattga atccccggtt taataattcc aacacctgga tcatttctga atctgattct 420
tttgattgct ctatttcttg acagagtgtg ttttaatgct tgatcctcca cagtttaatt 480

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00131PCT1.ST25.txt

attattggct gactgtcaga tttcttttgt ttgacagtag aaattatagt atatattttt 540
 tttcctgaa aatagacatt cattttttt 568

<210> 62
 <211> 686
 <212> DNA
 <213> Homo sapiens

<400> 62
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 gctgggggat agatggggag gcagaaatag cttgggaaaa ggaagcagga aaaaaggaaa 120
 tctttatggg aaatcaatta cccaaagcaa ggtgagtcac ctagagggtga atatgatgtt 180
 gttattgtcc tcccttagtg tacagcacag tttttgctct cacagggttt ttctctttag 240
 gatgcgtagc accctatgca ttaaatacat agcatcctaa agacacccta ctcaccatga 300
 gtctgtaggc tctttcctga tgagggcact ggccatatat gaatggaaaa ctcaactcat 360
 ctctcagct ttagatgttg ctgctgttca gctggatttg tgagaaatat ctggattact 420
 atcaagaaca tttagcaaga ctcaaaagag agaggcaagc agaaccaaaa cccaaacctc 480
 aaccaatgac tagctgaata aacaattctt tggaggaata aggaaggat tcttgatgt 540
 attctgagaa tgctcttcca aaagggaaga tggtaataat ggacttggtt tgatttcatg 600
 gttgtgatag aatgtacttc catgatgtga aatacacttc tggcagataa aatgcagggt 660
 gtaatttgca tttgtacatc acagggt 686

<210> 63
 <211> 565
 <212> DNA
 <213> Homo sapiens

<400> 63
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 ggccttattt ttggcagtgg ggagaaatgag aagtcaccct ggctgagatg agaagatagg 120
 ggagagttct gagcagaagt gaggcgttgc ccaagttgct gcggaaaagg ttcacctggg 180
 tgcctgtgcg caggtgggccc agaaagtacg caggtgcacg aagaaggaag cccgtgagca 240
 aggcagggtg gctcagaccc ccagtggcgt agaccaaggc ggcagggcac aggttgggag 300
 aattggattt tggatctgtt ttgaataggg actccactga atgcattgtt ggattctctg 360
 tgtggtgtga gatctacaga ggtctaaaaa tggctccaaa agtttcatcc tgacagcctg 420
 agccactggc aggatggagt tgactttacc aaaacaggga agatgtcaag gggcccagga 480
 ttgggaaaag catgaacaag gactgtggtt gagtttcagg tgttgagttg cctctctgca 540
 tctctgcagc aaagcagaga catca 565

<210> 64
 <211> 627
 <212> DNA
 <213> Homo sapiens

00131PCT1.ST25.txt

<400> 64
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 cacatcaaac tgagatggag aagtcccatg ccatatatga cagatctacc aagctggctt 120
 tacaaaattc atctatgaag acccacaatc ctcccctccc cacacctagg gctttgccag 180
 tctaaagggtt cagccaagaa aaaaaagggtg ccacactagg actgtccttg attctgggaa 240
 catccttcag gaagacatcc caggctatta gccatgtgaa gttggccact tgcccctggt 300
 aactaccaca aatagccctt gttgaaaatt cagctaactc ctgattatcc actcagttcc 360
 ggaaaggcac agataaacc ctagagtggag taattaccaa tatctggctt tggaatgcaa 420
 tcttctgaaa taaaaaaaaa aacttacatc ttacctctgt gtaggaggtt tttttggttt 480
 ttttgttttg ttttgagatg gagtcttgct cttgtcacc aggcttggag tgcagtggca 540
 cgatctcagc tcaactgcaac ctccgcctcc ccggttcgag caattctcct gcctcagcct 600
 cctgagtagc tgggactaca ggcacac 627

<210> 65
 <211> 340
 <212> DNA
 <213> Homo sapiens

<400> 65
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 gtacttttac aaccccatc caaaaccca cagaccaaaa cctgaaggct agtaaggagg 120
 aacatgagtc aacaaatgac ctcatctcc atttgtttac aaactccact gatgtctgtg 180
 gtttccaact gatcattatt ttaaaaatgg gtgaaatagt gtgagatctc agagcacttt 240
 tcttttctct cttttctttt ttccctttttt tttttttttt tgagacagtc ttactctgtc 300
 tccccaggct ggagtgcagt ggcgagatca cagctcactg 340

<210> 66
 <211> 554
 <212> DNA
 <213> Homo sapiens

<400> 66
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 tggcaatcat taaaaagtca ggaaacaaca ggtgctggag aggatgtgga gaaataatat 120
 cttttttaac cttcttatac ataaataatt atgggtgactg agagaaaaag aacaatcaag 180
 aaagaagatc ctcaggatc ataatgtaga ttgaaaataa tgtcttttgt tcaaataaga 240
 aaggtaggca ggaaccagca gtggtgatga aaatggtggc tctgtgtatt tgtgggcat 300
 acaaatcaga aagggtgaatg ttcctggagc tccagagaaa tctagaggaa gataagagtt 360
 ggcttatcag catagagggtg gtaggtgagg acaggggatg aaataacaca caaaatatat 420
 aaaggtaagt agaagttgaa tatggaattc taagtgattg ggagattaaa aaaaatgaca 480
 cacagaaaag agtgaaccag gtcacataga aaaacattgc tttcttcaaa gacaagaaag 540

00131PCT1.ST25.txt

gagacagttt gaag

554

<210> 67
 <211> 630
 <212> DNA
 <213> Homo sapiens

<400> 67
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 agtgtacgtt gttcagccca tgatttctgt ttggctactt ttaagatttc ccatctcggt 180
 gttgaaattc tcactatatt ttgtgtcct tgatgagcat cttgtaatta tttttaatta 240
 tctattggat aaatcatgta aggttggttt ctgtatgttt atcttggtcc tttgtttaga 300
 acatttttac ctgattcttc attttttctt gaccctctat gttgggttct gtatattaac 360
 aaagcaagca cctctcccag tcttcatgga ctggttttat aaaagagaac actttcacca 420
 acaaatacag ccaaaaataa tgggtggccta taataattct ttccctcctg aggaggaatt 480
 aggcagctgt gatttttgtc catttattct gtgttgagcc agagagaggg tagctatggt 540
 ctacaagccc aaaacaccat tttcatactt ctctgagcag cttgactgtg ctgggcctgc 600
 ttaagtcagc actgggttaga aatgctagtt 630

<210> 68
 <211> 195
 <212> PRT
 <213> Homo sapiens

<400> 68
 Gln Lys Ser Leu Trp Phe Leu Phe Ser Leu Ser Ser Pro Ser His Cys
 1 5 10 15
 Ser Leu Ala Ile Gln Ala Trp Arg Leu Ser Gln Pro Ser Phe Leu Leu
 20 25 30
 Val Gly Ile Pro Gly Leu Glu Glu Ser Gln His Trp Ile Ala Leu Pro
 35 40 45
 Leu Gly Ile Leu Tyr Leu Leu Ala Leu Val Gly Asn Val Thr Ile Leu
 50 55 60
 Phe Ile Ile Trp Met Asp Pro Ser Leu His Gln Ser Met Tyr Leu Phe
 65 70 75 80
 Leu Ser Met Leu Ala Ala Ile Asp Leu Val Leu Ala Ser Ser Thr Ala
 85 90 95
 Pro Lys Ala Leu Ala Val Leu Leu Val His Ala His Glu Ile Gly Tyr
 100 105 110
 Ile Val Cys Leu Ile Gln Met Phe Phe Ile His Ala Phe Ser Ser Met
 115 120 125
 Glu Ser Gly Val Leu Val Ala Met Ala Leu Asp Arg Tyr Val Ala Ile
 130 135 140

00131PCT1.ST25.txt

Cys His Pro Leu His His Ser Thr Ile Leu His Pro Gly Val Ile Gly
145 150 155 160

Arg Ile Gly Met Val Val Leu Val Arg Gly Leu Leu Leu Leu Ile Pro
165 170 175

Phe Pro Ile Leu Leu Gly Thr Leu Ile Phe Cys Gln Ala Thr Ile Ile
180 185 190

Gly His Ala
195

<210> 69
<211> 206
<212> PRT
<213> Homo sapiens

<400> 69

Lys Ile Leu Arg Gly Ser Gln Gly Pro Glu Arg Asn Asn His Lys Glu
1 5 10 15

Leu His Ser Ser Arg Tyr Ile Phe Tyr Phe Phe Ser Leu Ile Ser Thr
20 25 30

Arg Cys Asn His Gln Tyr Cys Leu Asn Leu Leu Gln Asp Phe Gly Gly
35 40 45

His Pro Pro Ser Pro Leu Ser Pro His Thr Met Thr Leu Gly Ser Leu
50 55 60

Gly Asn Ser Ser Ser Ser Val Ser Ala Thr Phe Leu Leu Ser Gly Ile
65 70 75 80

Pro Gly Leu Glu Arg Met His Ile Trp Ile Ser Ile Pro Leu Cys Phe
85 90 95

Met Tyr Leu Val Ser Ile Pro Gly Asn Cys Thr Ile Leu Phe Ile Ile
100 105 110

Lys Thr Glu Arg Ser Leu His Glu Pro Met Tyr Leu Phe Leu Ser Met
115 120 125

Leu Ala Leu Ile Asp Leu Gly Leu Ser Leu Cys Thr Leu Pro Thr Val
130 135 140

Leu Gly Ile Phe Trp Val Gly Ala Arg Glu Ile Ser His Asp Ala Cys
145 150 155 160

Phe Ala Gln Leu Phe Phe Ile His Cys Phe Ser Phe Leu Glu Ser Ser
165 170 175

Val Leu Leu Ser Met Ala Phe Asp Arg Phe Val Ala Ile Cys His Pro
180 185 190

Leu His Tyr Val Ser Ile Leu Thr Asn Thr Val Ile Gly Arg
195 200 205

<210> 70
<211> 219
<212> PRT
<213> Homo sapiens

<400> 70

Ala Ile Ser Thr Lys Cys Cys Leu Ser Ile Leu Trp Pro Thr Ile Trp
1 5 10 15

00131PCT1.ST25.txt

Tyr Tyr Cys Ser His Ala Gly Ser Leu Ser Met Ile Met Cys Ala Leu
 20 25 30
 Leu Trp Ala Leu Ser Leu Leu Leu Lys Leu Leu Glu Gly Tyr Tyr Cys
 35 40 45
 Ala Val Cys Val Pro His Phe Leu Tyr Pro Ile Asn Tyr Gly Ala His
 50 55 60
 Phe His Val Phe Ala Ile Val Asn Arg Ile Ala Met Asn Ile Gln Val
 65 70 75 80
 Gln Val Ser Phe Asn Asp Leu Phe Ser Phe Gly Tyr Ile Pro Ser Ser
 85 90 95
 Glu Ile Thr Glu Ser Asn Ser Ser Ser Lys Leu Phe Gly Lys Ser Pro
 100 105 110
 Asn Cys Phe Pro Gln Trp Leu Asn Phe Thr Tyr Pro Pro Thr Thr Tyr
 115 120 125
 Lys His Ser Leu Phe Ser Ala Ala Ser Pro Ala Ser Val Val Phe Cys
 130 135 140
 Trp Arg Ala Ala Ala Ser Arg Leu Thr Ala Ile Ser Ala Ser Gln Val
 145 150 155 160
 Gln Ala Ile Leu Tyr Leu Ser Phe Leu Ser Ser Asp Tyr Arg His Pro
 165 170 175
 Pro Pro Cys Pro Ala Asn Phe Cys Ile Phe Ser Arg Asp Gly Val Ser
 180 185 190
 Ser Ser Trp Pro Gly Trp Ser Thr Pro Asp Leu Ile Ile His Pro Pro
 195 200 205
 Arg Pro Pro Lys Val Leu Gly Leu Gln Ala Ala
 210 215

<210> 71
 <211> 215
 <212> PRT
 <213> Homo sapiens

<400> 71

Glu Pro Ser Gln Leu Arg Pro Ser Pro Val Arg Arg Leu Phe Ile His
 1 5 10 15
 Leu Ala Ala Ala Asp Leu Leu Val Thr Phe Val Val Met Pro Leu Asp
 20 25 30
 Ala Thr Trp Asn Ile Thr Val Gln Trp Leu Ala Val Asp Ile Ala Cys
 35 40 45
 Arg Thr Leu Met Phe Leu Lys Leu Met Ala Thr Tyr Ser Ala Ala Phe
 50 55 60
 Leu Pro Val Val Ile Gly Leu Asp Arg Gln Ala Ala Val Leu Asn Pro
 65 70 75 80
 Leu Gly Ser Arg Ser Gly Val Arg Lys Leu Leu Gly Ala Ala Trp Gly
 85 90 95
 Leu Ser Phe Leu Leu Ala Phe Pro Gln Val Ser Asp Leu Gly Leu Arg
 100 105 110

00131PCT1.ST25.txt

Thr Gly Gln Asp Arg Asp Leu Gly Pro His Glu Leu Lys Gly Ala Leu
 115 120 125

Gly Gly His Pro Leu Ile Leu Arg Glu Ala Ser Ala Cys Phe Phe Phe
 130 135 140

Phe Leu Pro Ala His Cys Asn Leu Arg Leu Pro Gly Ser Ser Asn Ser
 145 150 155 160

Pro Pro Ser Ala Ser Arg Glu Ala Thr Gly Ala Arg Tyr His Ala Arg
 165 170 175

Leu Ile Phe Val Phe Leu Val Glu Ala Arg Phe His His Val Gly Gln
 180 185 190

Val Val Ser Ile Ser Pro His Asp Pro Pro Val Ser Ala Ser Gln Ser
 195 200 205

Ala Glu Ile Gln Ala Ala Thr
 210 215

<210> 72
 <211> 143
 <212> PRT
 <213> Homo sapiens

<400> 72

Gln Gly Ser Cys Leu Cys Thr Leu Ala Trp Thr Thr Glu Asp Pro Ser
 1 5 10 15

Leu Asn Thr Lys Lys Lys Arg Val His Gly Asn Ile Ala Val Ile Ile
 20 25 30

Met Leu Tyr His Phe Ile Gly Thr Ala Cys Met Asp Ile Arg Gly Arg
 35 40 45

Gly Gly Gly Val Leu Gly Leu Ile Pro Gln Gly Tyr Gly Thr Thr Asn
 50 55 60

Tyr Gly Pro Gln Thr Arg Cys Ser Val Asn Glu Glu Leu Ser Ser Glu
 65 70 75 80

Met Arg Glu Ala Gly Arg Arg Trp Lys Leu Gly Lys Ala Leu Trp Glu
 85 90 95

Arg Trp Gln Met Ser Arg Ser Asn Arg Ile Gln Met Gly Val Trp Gly
 100 105 110

Gly Lys Glu Glu Asp Thr Ala Gln Lys Glu Lys Ser Thr Ala Ile Pro
 115 120 125

Arg Met His Leu Ile Leu Ala Asp Leu Arg Ser Ala Gly Leu Gly
 130 135 140

<210> 73
 <211> 187
 <212> PRT
 <213> Homo sapiens

<400> 73

Gly Lys Gly Gly Asn His Ser Cys Leu Leu Arg Phe Pro Ala Gly Gly
 1 5 10 15

Pro Lys Trp Gln Val Leu Tyr His Leu Gln Lys Ile Ala Val Ala Phe
 33

00131PCT1.ST25.txt

20 25 30
 Val Leu Pro Leu Ala Thr Leu Gly Thr Cys Ser Leu Leu Leu Arg Phe
 35 40 45
 Leu Arg Leu Trp Cys Ala Arg Trp Pro Ser Arg Val Arg Arg Arg Leu
 50 55 60
 Arg Ser Arg Val Thr Cys Ala Leu Ala Cys Val Leu Leu Ala Phe Val
 65 70 75 80
 Leu Cys Trp Leu Pro Ser Gln Ala Phe Thr Leu Gly Val Leu Ile Lys
 85 90 95
 Leu Asn Ala Met Pro Leu Asp Arg Ala Tyr Phe Leu Ala Gln Ala Tyr
 100 105 110
 Leu Phe Pro Val Ser Ile Cys Leu Thr His Cys Asn Asn Ser Leu Asn
 115 120 125
 Pro Leu Leu Tyr Cys Leu Leu Arg Arg His Phe Arg Gln Gly Leu Arg
 130 135 140
 Glu Leu Cys Ser Ala Gln Arg Pro Val Pro Leu Arg Ala Ser Ser His
 145 150 155 160
 Gly Ser Ala Pro Ala Ala Ala Leu Phe Gln Gly Pro Ala Cys Arg Cys
 165 170 175
 Val Ser Thr Lys Gly Met Gly Lys Trp Leu Ile
 180 185

<210> 74
 <211> 172
 <212> PRT
 <213> Homo sapiens

<400> 74

Ser Phe Ser Tyr Pro Ser Phe Gln Thr His Val Leu Tyr Gln Ser Ser
 1 5 10 15
 Phe Phe Ser Leu Leu Leu Ser Leu Ile Arg Pro Met Leu Ile Cys Ala
 20 25 30
 Gly Phe Leu Ile Ala Trp Ile Pro Tyr Ala Val Val Ser Val Trp Ser
 35 40 45
 Ala Phe Gly Arg Pro Asp Ser Ile Pro Ile Gln Leu Ser Val Val Pro
 50 55 60
 Thr Leu Leu Ala Lys Ser Ala Ala Met Tyr Asn Pro Ile Ile Tyr Gln
 65 70 75 80
 Val Ile Asp Tyr Lys Phe Ala Cys Cys Gln Thr Gly Gly Leu Lys Ala
 85 90 95
 Thr Lys Lys Lys Ser Leu Glu Gly Phe Arg Asn Phe Arg Ser Trp Lys
 100 105 110
 Ile Thr Leu Ser Leu Phe Gln Asn Pro Ala Gly Phe Lys Val Leu Arg
 115 120 125
 Cys Ala Val Phe Leu Gly Leu Lys Leu Ile Ala Glu Cys Arg Lys Asp
 130 135 140
 Phe Ile Phe Cys Leu Ser Lys Phe Leu Lys Ser Ser Asn Gln Leu Cys
 34

00131PCT1.ST25.txt

145 150 155 160
 Arg Gly Cys Met Thr Trp Ile Asp Ser Glu Lys Phe
 165 170

<210> 75
 <211> 187
 <212> PRT
 <213> Homo sapiens

<400> 75

Gly Val Ile Tyr Asp Cys Thr Ile Ala Leu Gln Pro Gly Gln Asn Val
 1 5 10 15
 Thr Leu Ser Gln Lys Glu Ser Phe His Lys Lys Tyr Gln Met Glu Lys
 20 25 30
 Ile Ile Ser Gly Val Ser Glu Gly Thr Arg Gly Cys Ser Asp Arg Gln
 35 40 45
 Pro Gly Ala Leu Thr Gln Gly His Ser Cys Ser Arg Lys Met Asn Ala
 50 55 60
 Ser Arg Cys Leu Ser Glu Glu Val Gly Ser Leu Arg Pro Leu Thr Met
 65 70 75 80
 Ala Val Leu Ser Ala Ser Phe Val Val Gly Val Leu Gly Asn Gly Leu
 85 90 95
 Val Pro Trp Val Thr Val Phe Arg Met Ala Arg Thr Val Ser Thr Val
 100 105 110
 Cys Phe Phe His Leu Ala Leu Ala Asp Phe Met Leu Ser Leu Ser Leu
 115 120 125
 Pro Ile Leu Val Tyr Tyr Ile Val Ser Arg Gln Trp Leu Leu Gly Glu
 130 135 140
 Trp Ala Cys Lys Leu Tyr Thr Gly Phe Val Phe Leu Thr Phe Ser Thr
 145 150 155 160
 Ser Asn Cys Leu Leu Val Leu Ile Ser Val Asp Arg Cys Ile Ser Val
 165 170 175
 Leu Tyr Pro Val Trp Ala Leu Asn His Arg Thr
 180 185

<210> 76
 <211> 194
 <212> PRT
 <213> Homo sapiens

<400> 76

Lys Thr Asn Ile Phe Val Tyr Pro Asn Met Asn His Ala Leu Asp Ser
 1 5 10 15
 Asn Phe Thr Leu Phe Ser Ala Glu Ile Val Ile Leu Met Leu Tyr Gly
 20 25 30
 Arg Asn Ile Ser Leu Gln Asp Gly Asn Asn Ser Thr Asn Ser Thr Arg
 35 40 45
 Ala Lys Cys Thr Asp Leu Gln Met Pro Phe Gln Tyr Ser Leu Tyr Lys
 50 55 60

00131PCT1.ST25.txt

Thr Thr Tyr Ile Leu Ile Phe Ile Pro Gly Leu Leu Ala Asn Thr Val
 65 70 75 80
 Ala Val Trp Val Leu Cys His Phe Ile Asn Lys Lys Asn Lys Val Ile
 85 90 95
 Ile Phe Ile Ile Asn Leu Ser Val Ala Asp Leu Ala His Met Leu Ser
 100 105 110
 Leu Pro Leu Trp Ile Tyr Tyr Tyr Ile Ser His His Trp Pro Phe Gln
 115 120 125
 Gly Pro Leu Asp Leu Val Cys Phe Tyr Leu Lys Tyr Leu Asn Ile Tyr
 130 135 140
 Thr Ser Ile Cys Phe Leu Thr Cys Ile Ser Leu Gln Arg Cys Phe Phe
 145 150 155 160
 Leu Leu Lys Cys His Ile Leu Glu Ala Val Arg Gly Ser Ser Trp Arg
 165 170 175
 Leu Leu Val Tyr His Phe Pro Phe Glu Ala Leu Ala Ser Gln Gln His
 180 185 190

Gln Ile

<210> 77
 <211> 156
 <212> PRT
 <213> Homo sapiens

<400> 77

Phe Ser Ser Leu Phe Thr Ala His Trp Trp Val Ile Ser Leu Asp Gln
 1 5 10 15
 Tyr Arg Ser Leu Thr Val Val Lys Tyr Asn Leu Lys Ser Thr Gln Trp
 20 25 30
 Ser Ile Lys Val Ser Ile Arg Met Val Gln Met Ile Ser Asp Leu Ile
 35 40 45
 Ser Phe Pro Ser Trp Ile Thr Arg Tyr Glu Ile Gly Gly Arg His Phe
 50 55 60
 Ser Gln Gln Ala Lys Leu Leu Phe Gly Gln Asn His Ile Leu Ile Leu
 65 70 75 80
 Gly Tyr Gly Ser Leu Gln Ile Thr Phe Phe Val Asn Phe Phe Leu Cys
 85 90 95
 Ser Lys Ile Lys Leu Pro Ile Ser Asp Ser Gln Cys Gln Phe Met Asn
 100 105 110
 Thr Phe Ile Lys Leu Lys Glu Val Asn Leu Asp Gly Glu Gly Leu Gly
 115 120 125
 Val Ile Phe Lys Arg Ile Gly Cys Ser Gly Tyr Thr Lys Arg Asp Gln
 130 135 140
 Gly Gly Ser Met Val Pro Leu Phe Lys Tyr Leu Lys
 145 150 155

<210> 78
 <211> 201
 <212> PRT

00131PCT1.ST25.txt

<213> Homo sapiens

<400> 78

Val Ala Gly Ile Glu Val Val Lys Thr Val Val Lys Asn Met Asp Lys
 1 5 10 15
 Lys Thr Arg Arg Gly Gly Arg Gly Ala Arg Ala His Gly Gly Gly Gly
 20 25 30
 Gly Ile Ser Pro Thr Glu Asn Gly Thr Ser Ser Arg Asp Met Lys Ala
 35 40 45
 Val Cys Ser His His Lys Lys Gly Ser Gly Asp Asn Leu Ser Ser Leu
 50 55 60
 Cys Ser Leu Lys Val Ala Ile Tyr Leu Gly Tyr Phe Val Ala Trp Arg
 65 70 75 80
 Met Cys Leu His Cys His Cys Leu Trp Arg Val Pro Arg Pro Cys Leu
 85 90 95
 Thr Ile Val Met Thr Leu Trp Arg Gly Ser Ser Leu Leu Leu Thr Ser
 100 105 110
 Phe Pro Ser Ser Thr Gln Leu Ser Ser Ala Trp Leu Ala Met Ala Leu
 115 120 125
 Ser Phe Gly Leu Asp Ser Thr Cys Pro Ala Gln Ser Thr Arg Cys Gly
 130 135 140
 Trp Tyr Leu Asn Leu Pro Val Ala Asp Phe Ile Ile Ile Phe Pro Leu
 145 150 155 160
 Leu Leu Gln Leu Val Met Val Ala Leu Pro Phe Gly Gln Leu Leu Cys
 165 170 175
 Lys Leu Asn Ser Thr Met Ser Ile Phe Asn Phe Leu Ala Ser Val Phe
 180 185 190
 Leu Leu Thr Leu Ile Phe Met Asp His
 195 200

<210> 79

<211> 220

<212> PRT

<213> Homo sapiens

<400> 79

Asp Lys Ser Ser Leu Gly Ser Phe Lys Leu Ser Leu Phe Ile Asp Asn
 1 5 10 15
 Cys Trp Ala Phe Ile Asn Leu Gly Asn Leu Cys Asn Gln Gly Cys Val
 20 25 30
 Cys Ala Phe Thr Cys Val Pro Val Leu Gly Arg Arg Phe Arg Val Glu
 35 40 45
 Val Gly Gly Glu Ile Val Thr Arg Gly Thr Ser Val Asp Lys Ser Leu
 50 55 60
 Gly Ala Leu Val Val Gly Lys Pro Phe Thr Ile Ile Ser Cys Phe Cys
 65 70 75 80
 His Arg Trp Val Phe Gly Trp Ile Gly Cys Arg Trp Tyr Gly Trp Ala
 85 90 95

00131PCT1.ST25.txt

Gly Phe Phe Phe Gly Cys Gly Ser Leu Ile Thr Met Thr Ala Val Ser
 100 105 110
 Leu Asp Arg Tyr Leu Lys Ile Cys Tyr Leu Ser Tyr Gly Lys Leu Ala
 115 120 125
 Gly Phe Ser Phe Pro Asp Ser Ser Val Asp Val Leu Glu Leu Tyr Ile
 130 135 140
 Phe Tyr Ala Gly Asn Lys Gln Arg Leu Ile Thr Ser Glu Ile Lys Asn
 145 150 155 160
 Ile Ser Ile Tyr Ser Leu Ser Ser Cys Ser Asp Met Phe Lys Asp Phe
 165 170 175
 Asn Leu Cys Gln Ser Arg Phe Leu Leu Ile His Ile Leu Cys Leu Val
 180 185 190
 Phe Gly Tyr Asn Ala Leu Lys Lys Tyr His Phe Leu Val Cys Val Ser
 195 200 205
 Phe His His Val Ser His Ala Asn Lys Arg Asn Lys
 210 215 220

<210> 80
 <211> 176
 <212> PRT
 <213> Homo sapiens

<400> 80

Ser Tyr Cys Gln Thr His Thr Val Thr His Ser Phe Cys Leu His Gln
 1 5 10 15
 Asp Ile Met Lys Leu Ser Cys Thr Asp Thr Arg Val Asn Val Val Tyr
 20 25 30
 Gly Leu Phe Ile Ile Leu Ser Val Met Gly Val Asp Ser Leu Phe Ile
 35 40 45
 Gly Phe Ser Tyr Ile Leu Ile Leu Trp Ala Val Leu Glu Leu Ser Ser
 50 55 60
 Arg Arg Ala Ala Leu Lys Ala Phe Asn Thr Cys Ile Ser His Leu Cys
 65 70 75 80
 Ala Val Leu Val Phe Tyr Val Pro Leu Ile Gly Leu Ser Val Val His
 85 90 95
 Arg Leu Gly Gly Pro Thr Ser Leu Leu His Val Val Met Ala Asn Thr
 100 105 110
 Tyr Leu Leu Leu Pro Pro Val Val Asn Pro Leu Val Tyr Gly Ala Lys
 115 120 125
 Thr Lys Glu Ile Cys Ser Arg Val Leu Cys Met Phe Ser Gln Gly Gly
 130 135 140
 Lys Asp Thr Leu Val Ser Ser Leu Leu Leu Leu Leu Gln Lys Met Gly
 145 150 155 160
 Ile Leu Gly Ser Leu Leu Asn Ala Trp Leu Lys Tyr Gln Thr Tyr Cys
 165 170 175

<210> 81
 <211> 221

00131PCT1.ST25.txt

<212> PRT
 <213> Homo sapiens

<400> 81

Leu Pro Gly Gln Arg Ile Arg Glu His Pro Gly Pro Glu Ser Pro Gln
 1 5 10 15
 Pro Ala Trp Pro Gly Arg Gly Gly Gly Arg Pro Gly Ala Gly Ala
 20 25 30
 Ala Gly Ser Asp Cys Gly Arg Leu Leu Gly Pro Val Arg Cys Arg Pro
 35 40 45
 Gly Gly Gln Arg Leu Val Leu Val Arg Val Arg Ser Gln Gln Trp Arg
 50 55 60
 Arg His Trp Leu Leu Asn Cys Phe Leu Leu Asn Leu Ala Ala Thr Asp
 65 70 75 80
 Leu Gln Phe Val Leu Thr Leu Pro Phe Trp Ala Val Asp Thr Val Arg
 85 90 95
 Asp Phe Ser Trp Pro Phe Gly Gly Ala Ile Cys Lys Val Met Leu Thr
 100 105 110
 Leu Thr Val Leu Asn Met Tyr Ala Ser Ile Phe Leu Leu Ser Ala Met
 115 120 125
 Ser Val Ala Arg Tyr Cys Ile Val Thr Gly Ala Leu Pro Pro Ser His
 130 135 140
 Arg Gly Ala Ser Arg Ala Ser Cys Val Cys Cys Leu Leu Trp Ala Thr
 145 150 155 160
 Ala Val Leu Ala Thr Ala Pro Thr Ala Leu Phe Ala Thr Ala Ala Arg
 165 170 175
 Val Gly Gly Lys His Ser Cys Leu Leu Arg Phe Pro Ala Gly Gly Pro
 180 185 190
 Lys Trp Gln Val Leu Tyr His Leu Gln Lys Ile Thr Val Ala Phe Val
 195 200 205
 Leu Pro Leu Ala Thr Leu Gly Thr Cys Ser Leu Leu Leu
 210 215 220

<210> 82
 <211> 248
 <212> PRT
 <213> Homo sapiens

<400> 82

Leu Thr Cys Ala Met Leu Val His Gly Asp Val Pro Glu Asn Gln Leu
 1 5 10 15
 Lys Trp Thr Val Phe Val Arg Ala Leu Ile Asn Asp Ser Leu Phe Ile
 20 25 30
 Leu Cys Ala Ile Ser Leu Val Cys Tyr Ile Cys Lys Ile Thr Lys Met
 35 40 45
 Ser Ser Ala Asn Val Tyr Leu Glu Ser Lys Gly Met Ser Leu Cys Gln
 50 55 60
 Thr Val Val Val Gly Ser Val Val Ile Leu Leu Tyr Ser Ser Arg Ala
 39

65				70				75				80			
Cys	Tyr	Asn	Leu	Val 85	Val	Val	Thr	Ile	Ser 90	Gln	Asp	Thr	Leu	Glu 95	Ser
Pro	Phe	Asn	Tyr 100	Gly	Trp	Asp	Asn	Leu 105	Ser	Asp	Lys	Ala	His 110	Val	Glu
Asp	Ile	Ser 115	Gly	Glu	Glu	Tyr	Ile 120	Val	Phe	Gly	Met	Val 125	Leu	Phe	Leu
Trp	Glu 130	His	Val	Pro	Ala	Trp 135	Ser	Val	Val	Leu	Phe 140	Phe	Arg	Ala	Gln
Arg 145	Leu	Asn	Gln	Asn	Leu 150	Ala	Pro	Ala	Gly	Met 155	Ile	Asn	Ser	His	Ser 160
Tyr	Ser	Ser	Arg	Ala 165	Tyr	Phe	Phe	Asp	Asn 170	Pro	Arg	Arg	Tyr	Asp 175	Ser
Asp	Asp	Asp	Leu 180	Pro	Arg	Leu	Gly	Ser 185	Ser	Arg	Glu	Gly	Ser 190	Leu	Pro
Asn	Ser	Gln 195	Ser	Leu	Gly	Trp	Tyr 200	Gly	Thr	Met	Thr	Gly 205	Cys	Gly	Ser
Ser	Ser 210	Tyr	Thr	Val	Thr	Pro 215	His	Leu	Asn	Gly	Pro 220	Met	Thr	Asp	Thr
Ala 225	Pro	Leu	Leu	Phe	Thr 230	Cys	Ser	Asn	Leu	Asp 235	Leu	Asn	Asn	His	His 240
Ser	Leu	Tyr	Val	Thr 245	Pro	Gln	Asn								

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<210> 83
<211> 215
<212> PRT
<213> Homo sapiens
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<222>  (99)..(100)
<223>  Xaa is any Amino Acid
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<220>
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<222>  (149)..(149)
<223>  Xaa is any Amino Acid
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<400> 83

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00131PCT1.ST25.txt

65 70 75 80
 Asn Trp Cys Gln Ile Leu Asp Phe Leu Thr Ala Val Trp Leu Ile Phe
 85 90 95
 Leu Ile Xaa Xaa Ser Val Val Leu Cys Gly Phe Thr Leu Val Leu Leu
 100 105 110
 Val Arg Ile Ile Cys Gly Ser Gln Lys Met Pro Leu Thr Arg Leu Tyr
 115 120 125
 Val Thr Ile Leu Leu Thr Gly Leu Val Phe Leu Phe Cys Ser Leu Pro
 130 135 140
 Leu Ser Ile Gln Xaa Phe Leu Leu Tyr Trp Ile Glu Lys Asp Leu Asp
 145 150 155 160
 Asp Leu Pro Cys Val Val Arg Leu Ile Ser Ile Phe Leu Ser Ala Leu
 165 170 175
 Asn Ser Ser Ala Asn Pro Ile Ile Tyr Phe Phe Met Gly Ser Phe Arg
 180 185 190
 Gln Leu Gln Asn Arg Lys Thr Leu Lys Leu Val Leu Gln Arg Ala Leu
 195 200 205
 Gln Asp Met Leu Glu Val Asp
 210 215

<210> 84
 <211> 166
 <212> PRT
 <213> Homo sapiens

<400> 84

Gly Asp Phe Met Leu Asn Arg Glu Leu Ile Pro Asn Ser Val Leu Val
 1 5 10 15
 His Glu Ser Cys Val Phe Cys Lys Ile Phe Pro Tyr Phe Arg Lys Pro
 20 25 30
 Leu Lys Phe Phe Trp Phe Leu Thr Met Lys Cys Val Ser Pro Ile Ser
 35 40 45
 Lys His Leu Met Gln Asn Met Ala His His Leu Leu Arg Trp Lys Phe
 50 55 60
 Thr Ile Tyr Ile Thr Val Arg Ile Met Thr His Ser Thr Tyr Phe Val
 65 70 75 80
 Thr Cys Phe Lys Met Val Ala Glu Ser Thr Val Glu Lys Ala Ala Leu
 85 90 95
 Ile Asn Thr Tyr Glu Lys Ile Asn Asn Ile Ser Ile Gly Thr Ile Lys
 100 105 110
 Lys Val Phe Ser Ile Ile Leu Ile Phe Ile Phe Lys Ile Ser Ser Trp
 115 120 125
 Ala Arg Trp Leu Thr Pro Val Thr Pro Ala Phe Phe Phe Phe Phe Leu
 130 135 140
 Arg Trp Ser Leu Pro Leu Ser Pro Asp Trp Ser Ala Gly Arg Ile Ser
 145 150 155 160
 Ala His His Asn Leu Arg

00131PCT1.ST25.txt

165

<210> 85
 <211> 160
 <212> PRT
 <213> Homo sapiens

<400> 85

Lys Thr Ser Gly Phe Leu Arg Leu Leu Phe Met Tyr Ile Val Leu Thr
 1 5 10 15
 Ser Asn Glu Gln Leu Ser Phe Ser Asn Pro Val Ile Ser Val Ile Leu
 20 25 30
 Lys Gly Lys Arg Leu Glu Phe Leu Phe Leu His Ile Asn Tyr Ser His
 35 40 45
 Leu Thr Arg Leu Pro Thr Phe Leu Asp Leu Val Leu Lys Thr Ser Ile
 50 55 60
 Leu Leu Arg Leu Leu Tyr Gln Met Tyr Tyr Tyr Ser Thr Glu Asn Thr
 65 70 75 80
 Lys Gly Ile Cys Tyr Thr Tyr Ile Lys Glu Asp Phe Ile His Arg Gln
 85 90 95
 Thr Asp Ser Leu Leu Asp Leu Ile Lys Val Lys Pro Ile Val Lys Tyr
 100 105 110
 Gln Cys Gln Ile Arg Tyr Ile Leu Arg Leu Tyr Ser Leu Lys Lys Ser
 115 120 125
 Asp Asn Ile Gln Lys Phe Ala Phe Leu Phe Leu Leu His Phe Tyr Ile
 130 135 140
 Leu Ser His Arg Ala Cys Arg Lys Ser Thr Leu Thr Val Trp Thr Arg
 145 150 155 160

<210> 86
 <211> 131
 <212> PRT
 <213> Homo sapiens

<220>
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 <222> (60)..(60)
 <223> Xaa is any amino acid

<400> 86

Gly Leu Lys His Leu Ala Leu Gly Leu Ala His Asn Arg Cys Leu Lys
 1 5 10 15
 Ser Gly Ser Ser Cys Asn Leu Ser Ile Ile Tyr Ser Met Trp Ile Phe
 20 25 30
 Ile Leu Asn Val Ile Ile Ala Met Gly Leu Pro Leu Ser Thr Ile Thr
 35 40 45
 Leu Leu Lys Leu Ile Met Val Ala Lys Ser Pro Xaa Ile Lys Thr His
 50 55 60
 Ser Leu Phe Cys Phe His Lys Tyr Leu Leu Ser Leu Tyr Tyr Met Ser
 65 70 75 80

00131PCT1.ST25.txt

Cys Thr Val Phe Arg Val Gly Gly Ile Thr Val Lys Lys Thr Asn Ile
85 90 95

Val Pro Gly Phe Met Gln Leu Ser Gln Cys Leu Arg Val Asp Leu Cys
100 105 110

Pro Gln Ser Pro Lys Asn Ser Trp Asn Ser Asn Ser Lys Tyr Lys Gln
115 120 125

Arg Ile Tyr
130

<210> 87
<211> 230
<212> PRT
<213> Homo sapiens

<400> 87

Ile Asp Val Ile Asn Ser Ala Gln Pro Leu His Lys Ser Arg Ala Leu
1 5 10 15

Arg Leu Lys Gln Thr Val Ser Ala Ile Phe Ile Phe His Ser Leu Ile
20 25 30

Thr Lys Ile Pro Leu Asn Ala Tyr Trp Met Val Asn Phe Leu Ile His
35 40 45

Ser Glu Arg Glu Glu Glu Ala Gly Leu Val Phe Asp Thr Lys Pro Val
50 55 60

Leu Lys Leu Lys Ala Lys His Ser Cys Glu Ser Trp His Ser Phe Leu
65 70 75 80

Ala Val Arg Pro Trp Arg Ile Leu Thr Leu Pro Ser Ser Thr Trp Arg
85 90 95

Tyr Ile Asn Ser Gly Ser Ser Leu Lys Gly Phe Ala Asp Cys Leu Lys
100 105 110

Leu Thr Gln Tyr Pro Tyr Tyr Leu Pro Pro Pro Gly Glu Ala Ala Asp
115 120 125

Thr Phe Met Glu Cys Tyr Ser Gln Ala Glu Glu Ser Leu Gly Asp Ser
130 135 140

Leu Leu Leu Cys Cys Asp Pro Phe Cys Ser Val Pro Leu Ser Thr Tyr
145 150 155 160

Pro Asp Leu Leu Ala Tyr Ala Trp Ser Trp Gly Ile Asp Ala Phe Leu
165 170 175

Ala Leu Cys Phe Ile Ser Glu Tyr Ser His Leu Asn Pro Met Cys Tyr
180 185 190

Ser Leu Cys Asn Leu Arg Ser Cys Ser Arg Leu Lys Asn His Asn Pro
195 200 205

Tyr Ser Lys Leu Lys Ala Pro Lys Ile Val His Thr Lys Gln Met Cys
210 215 220

Thr Val Pro Arg Gln Leu
225 230

<210> 88
<211> 227
<212> PRT

00131PCT1.ST25.txt

<213> Homo sapiens

<400> 88

Phe Ala Lys Gln Phe Thr Lys Tyr Phe Tyr Ile Ser Lys Leu Arg Leu
 1 5 10 15
 Ile Ile Lys Ile Lys Thr Lys Lys Phe Ser Asn Tyr Ile Thr Ser Thr
 20 25 30
 Ile Leu Cys Val Lys Lys Asn Ile Phe Trp Ile Thr Asp Ile Phe Ile
 35 40 45
 Ile Ile Glu Cys Leu Ile Asn Asn Ser Ala Ile Arg Lys Ile Val Cys
 50 55 60
 Pro Phe Ser Thr Met Ser Tyr Ile Met Leu Pro Leu Lys Thr Asn Thr
 65 70 75 80
 Ile Tyr Val Ser Gly Glu Ile Val Leu Leu Thr Thr Ile Ile Ser Phe
 85 90 95
 Asn Leu Thr Phe Ile Lys Thr Asn Ile Phe Asp Asn Met Asn Phe Phe
 100 105 110
 Ile Leu Lys Gln Val Phe Leu Met Phe Leu Asn Glu Asn His Phe Cys
 115 120 125
 Gln Gln Lys Met Lys Lys Glu Lys Phe Asp Asn Ser Lys Phe Leu Leu
 130 135 140
 Tyr Ala Thr Lys Asn Gly Arg Asp Met Phe Phe His Thr Ile Asn Asp
 145 150 155 160
 Lys Ser Cys Leu Val Tyr Lys Glu Leu Arg Ala Leu Lys Thr Val Ser
 165 170 175
 Ile Lys Lys Ser Tyr Ser Leu Ser Trp Leu Pro Phe Phe Ser Gln Asn
 180 185 190
 Val Ser Asp Pro His Phe Gln Asn Arg Val Glu Ala Ile Tyr Met Asn
 195 200 205
 Phe Leu Leu Val Asn Leu Arg Arg Leu Tyr Leu Lys Phe Leu Cys Val
 210 215 220
 Ala His Ile
 225

<210> 89

<211> 112

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<222> (6)..(6)

<223> Xaa is any amino acid

<220>

<221> misc_feature

<222> (85)..(85)

<223> Xaa is any amino acid

<220>

00131PCT1.ST25.txt

<221> misc_feature
<222> (94)..(94)
<223> Xaa is any amino acid

<220>
<221> misc_feature
<222> (104)..(104)
<223> Xaa is any amino acid

<400> 89

Leu Leu Pro Cys Gln Xaa Ala Gln Pro Arg Ser Arg Val Glu Val Thr
1 5 10 15
Pro Arg Ser Arg Ile Ile Leu Ile Leu Val Asn Leu Val Leu Phe Val
20 25 30
Val Gly Ile Leu Gly Arg Arg Thr Thr Gln Arg Ser Pro Met Ser Cys
35 40 45
Arg Lys Lys Gly Tyr Leu Gln Lys Glu Leu Thr Asp His Ile Glu Ser
50 55 60
Ile Ala Tyr Ser Asn Ile Leu Val Phe Phe Ile Gly Met Pro Thr Gly
65 70 75 80
Ser Ser Asp Leu Xaa Leu Asp Gln Thr Leu Phe Arg Tyr Xaa Ile Ile
85 90 95
Ser Leu Leu Tyr Thr Leu Tyr Xaa Ile Arg Tyr Ile Ile Asn Ala Asn
100 105 110

<210> 90
<211> 162
<212> PRT
<213> Homo sapiens

<220>
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<222> (75)..(75)
<223> Xaa is any amino acid

<220>
<221> misc_feature
<222> (91)..(91)
<223> Xaa is any amino acid

<220>
<221> misc_feature
<222> (135)..(135)
<223> Xaa is any amino acid

<400> 90

Val Ser Val Ser Lys Thr Gln Ala Leu Glu His Leu Phe Ile Ser Gly
1 5 10 15
Lys Arg Leu Glu Ala Ala Ala Trp Leu Phe Met His Gly Thr Val Phe
20 25 30
Leu Pro Leu Phe Phe Leu Leu Gln Ser Leu Ser Ser Leu Ala Met Met
35 40 45 45

00131PCT1.ST25.txt

Ile Glu Phe Pro Gly Gln Asn Asn Pro Leu Phe Phe Asn Trp Lys Ile
 50 55 60

Leu Ala Lys Cys His Asn Val Leu Val Ser Xaa Lys Leu Asn Ile Leu
 65 70 75 80

Gly Leu Arg Asn Phe Pro Gly Glu Arg Gln Xaa Asp His Ser Leu His
 85 90 95

Arg Ala Phe Cys Val Ala Val Thr Ala Arg Thr Lys Thr Ile Thr Leu
 100 105 110

Met Leu Phe Val Arg Met Gly Leu Phe Cys Cys Cys Phe Phe Met Val
 115 120 125

Val Phe His Tyr Ser Val Xaa Ile Cys Lys Asp His Cys Leu Phe Pro
 130 135 140

Leu Arg Glu Thr Val Tyr Val Ser Lys Leu Thr His Pro Arg Tyr Tyr
 145 150 155 160

Leu Leu

<210> 91
 <211> 69
 <212> PRT
 <213> Homo sapiens

<220>
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 <222> (59)..(59)
 <223> Xaa is any amino acid

<220>
 <221> misc_feature
 <222> (69)..(69)
 <223> Xaa is any amino acid

<400> 91

Cys Ile Phe Gln Arg Phe Thr Lys Phe Tyr Cys Lys Thr Ser Ile Ile
 1 5 10 15

Leu His His Phe Val Thr Tyr Thr Pro Phe Arg Trp Phe Ile Ser Ile
 20 25 30

Leu Leu Phe Leu Arg Cys Pro Ile Phe Tyr Phe Asn Leu Gln Asn Asn
 35 40 45

Ile Tyr Arg Leu Ile Phe Arg Ser Ser Pro Xaa Phe Leu Tyr Tyr Ile
 50 55 60

Phe Pro Leu Cys Xaa
 65

<210> 92
 <211> 137
 <212> PRT
 <213> Homo sapiens

<220>
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 <222> (22)..(22)

00131PCT1.ST25.txt

<223> Xaa is any amino acid

<220>

<221> misc_feature

<222> (38)..(38)

<223> Xaa is any amino acid

<220>

<221> misc_feature

<222> (127)..(127)

<223> Xaa is any amino acid

<400> 92

His	Trp	His	Phe	Leu	Gly	Tyr	Thr	Gly	Ile	Val	Gln	Gly	Ser	Leu	Thr
1				5					10					15	

Leu	Phe	Gly	Val	Tyr	Xaa	Tyr	Phe	Ser	Val	Phe	Thr	Gly	Thr	Leu	Trp
			20					25					30		

Gly	Ala	Pro	Ala	Leu	Xaa	Gly	Ile	His	Trp	His	Ser	Val	Gly	Cys	Thr
		35					40					45			

Asn	Thr	Leu	Trp	Gly	Phe	Thr	Asp	Thr	Leu	Glu	Val	Trp	Trp	His	Ser
	50					55					60				

Val	Gly	Val	His	Trp	Pro	Phe	Leu	Gly	Ile	Thr	Asp	Ile	Gly	Gly	Ala
65					70					75					80

Leu	Ala	Leu	Tyr	Arg	Ala	His	Gly	His	Phe	Ser	Gly	Phe	Ile	Asp	Thr
			85						90					95	

Leu	Gly	Cys	Thr	Gly	Thr	Leu	Trp	Gly	Ser	Leu	Thr	Leu	Trp	Gly	Cys
			100					105					110		

Ala	Gly	Thr	Leu	His	Gly	Ser	Leu	Val	Leu	Ser	Arg	Val	His	Xaa	His
		115					120					125			

Phe	Gly	Gly	Thr	Leu	Ala	Leu	Ser	Gly
	130					135		

<210> 93

<211> 149

<212> PRT

<213> Homo sapiens

<220>

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<222> (5)..(5)

<223> Xaa is any amino acid

<220>

<221> misc_feature

<222> (50)..(50)

<223> Xaa is any amino acid

<220>

<221> misc_feature

<222> (85)..(85)

<223> Xaa is any amino acid

00131PCT1.ST25.txt

<220>
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 <222> (145)..(145)
 <223> Xaa is any amino acid

<400> 93

Pro Ala Gln His Xaa Leu Ala Leu Ser Gln Ser Tyr Ser Pro Ile Gln
 1 5 10 15
 Tyr Pro Leu Arg Ile Ser Gln Asp Ile Cys His Leu Leu Phe Leu Asn
 20 25 30
 Ile Ala Val Thr Phe Arg Glu Leu Arg Lys Val Asn Asn Met Phe Cys
 35 40 45
 Phe Xaa Asn Cys Leu Leu Glu Val Ile Ser Asn Ile Leu Thr Trp Asn
 50 55 60
 Gln Tyr Val Phe Cys Phe Leu Ile Pro Cys Leu Ile Phe Phe Asn Leu
 65 70 75 80
 Arg Gly Thr Ile Xaa Tyr Phe Ser Ile Cys Ile Pro Cys Glu Ile Ile
 85 90 95
 Lys Ser Asp Lys Leu Thr Tyr Pro Ser Cys His Ile Leu Thr Ile Phe
 100 105 110
 Leu Phe Asp Met Phe Leu Lys Ile Lys Leu Leu Leu Thr Leu Ala Lys
 115 120 125
 Ile Leu Thr Asn Leu Tyr Val Tyr Glu Ile Tyr Val Tyr Ile Phe Ile
 130 135 140
 Xaa Val Tyr Ile Ile
 145

<210> 94
 <211> 211
 <212> PRT
 <213> Homo sapiens

<400> 94

Ala Val Val Tyr Lys Leu Gly Thr Lys Val Pro Thr Gln Gly Cys His
 1 5 10 15
 Ala Ile Ser Tyr Ile Asn Pro Cys Asn Ile Val Leu Lys Lys Trp Leu
 20 25 30
 Leu Phe Leu Pro Asn Ser Phe Thr Ala Leu Phe Ile Leu Ile Asp Glu
 35 40 45
 Ser Thr Pro Val Val Ala Leu Lys Gln Ser Phe Glu Ala Leu Ser Leu
 50 55 60
 Thr Tyr Lys Val Pro Leu His Tyr Lys Leu Lys Asn Val Leu Pro Pro
 65 70 75 80
 Pro Ile Ile Lys Ile Phe Cys Gly Val Phe Asp Met Leu Leu Leu Leu
 85 90 95
 Pro Thr Val Arg Leu Gly Ile Ser Leu Leu Leu Ile Leu Pro Ile Phe
 100 105 110
 Thr Val Ser Ser Val Leu Ser Ser Ser Ile Asn His Leu Cys Ala Ser
 48

00131PCT1.ST25.txt

115 120 125
 Ile Thr Phe Tyr Pro Thr Arg Ser Arg Ser Cys Asn Leu Thr Ala Ala
 130 135 140
 Glu Phe Val Ser Thr Val Ile Arg Val Leu Glu Arg His Trp His Tyr
 145 150 155 160
 Asn Gln Thr Leu Gln Tyr Ala Met Pro Lys Glu Phe Leu Met Arg Trp
 165 170 175
 Ile Phe Phe Leu Ser Trp Gly Ile Pro Leu Ser Pro Thr Gln Ile His
 180 185 190
 Ala Ser Val Trp Phe Gln Lys Lys Pro Asp Phe Leu Glu Pro Gln Ser
 195 200 205
 Pro Asp Ser
 210
 <210> 95
 <211> 231
 <212> PRT
 <213> Homo sapiens
 <400> 95
 Thr Pro His Ile Val Ile Asp Val Arg Glu Thr Val Ile Asn Cys Arg
 1 5 10 15
 His Leu Gln Asn Ile His Phe Ile Cys Leu Leu Ile Ser Ile Tyr Arg
 20 25 30
 Cys Cys Ile Asn Thr Glu Lys Glu Glu Asn Tyr Tyr Ser Val Ile Leu
 35 40 45
 Asn Leu Met Gln Phe Arg Gln Ile Cys Val His Lys Ile Cys Met Leu
 50 55 60
 Tyr Ile Tyr His Met His Asn Ile Pro Ser Met Pro Thr Ile Cys Ser
 65 70 75 80
 Glu Ser Ala Thr Asp Phe Cys Asp Thr Ile Asn Val Lys Tyr Leu Arg
 85 90 95
 Phe Phe Cys Phe Phe Cys Gly Asp Phe Phe Leu Phe Leu Asn Trp Pro
 100 105 110
 Val Tyr Pro Ala Asn Tyr Glu Ser Thr Leu Val Pro Ile Phe Ser Tyr
 115 120 125
 Thr Leu Ile Leu Ser Ala Ile Tyr Trp Leu Arg Ala Leu Gly Ser Phe
 130 135 140
 Met Ala Thr Val Ile Val Ser Leu Gly Thr Arg Ile Tyr Glu Gly Phe
 145 150 155 160
 Tyr Phe Lys His Leu Leu His Ile Leu Ile Asn Ala Leu His Asn Val
 165 170 175
 Thr Phe Leu Ala Gln Ser Thr Leu Glu Val Pro Ile Thr Tyr Pro Phe
 180 185 190
 Asn Pro Ala Cys Met Lys Ser His Thr His Phe Ile Ser Met Lys Met
 195 200 205
 Ser Leu Leu Glu Asp His Phe Ser Leu Tyr Lys Tyr Lys Ser Met Ile
 49

00131PCT1.ST25.txt
220

210 215
Pro Leu Thr Ile Leu Thr Ala
225 230

<210> 96
<211> 226
<212> PRT
<213> Homo sapiens

<400> 96

Phe Leu Gln Trp Val Ala Gly Leu Trp Arg Glu Asn Ser Asn Gly Ser
1 5 10 15

Gly Thr Tyr Leu Thr Phe His Ile His Pro Thr Gly Leu Gln Arg Lys
20 25 30

Ile Leu Leu Leu Tyr Tyr Lys Gly Lys Asn Ser Tyr Gly Val Ser Glu
35 40 45

Lys His Asn Val Leu Gly Leu Glu Leu Asn His Thr Ile Ser Glu Arg
50 55 60

Phe Leu Pro Gly Thr Ile His Leu Thr Ile Asn His Ile Leu Lys Leu
65 70 75 80

Ser Ala Val Gln Met Asp Tyr Val His Pro Thr Gly Asn Ser Ile Gly
85 90 95

Glu Ala Val Thr Leu His Cys His His Glu Cys Lys Val Trp Gly Leu
100 105 110

Ile Thr Phe Ala Pro Thr Phe Cys Leu Leu Val Ser Pro His Cys Gln
115 120 125

Glu His Leu Thr Asn Ser Leu Trp Leu Arg Val Pro Tyr Ala Ala Cys
130 135 140

Trp Gly Asn Gln Trp Val Leu Lys Thr Cys Leu Trp Cys Ala Arg Arg
145 150 155 160

Leu Cys Leu Pro Ala Thr Leu Thr Cys Asp Leu Pro Pro Gln Cys Met
165 170 175

Ala Ser Tyr Thr Trp Val Ile Asn Ile Ala Ser Met Ile Arg Arg Ser
180 185 190

Phe His His Tyr Cys His Ser Phe Arg Leu Pro Val Pro Cys Phe Phe
195 200 205

Leu Tyr Trp Asn Pro Arg Thr Ser Lys His Ser Ile Phe Lys His Pro
210 215 220

Ala Pro
225

<210> 97
<211> 134
<212> PRT
<213> Homo sapiens

<220>
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<222> (8)..(8)
<223> Xaa is any amino acid

00131PCT1.ST25.txt

<220>
<221> misc_feature
<222> (60)..(60)
<223> Xaa is any amino acid

<220>
<221> misc_feature
<222> (101)..(101)
<223> Xaa is any amino acid

<400> 97

Phe Tyr Phe Ile Gln Leu Pro Xaa Asn Asp Ser His Phe Ile Phe Ser
1 5 10 15
Ser Trp Thr Leu Gln Lys Asn Ala Ala Ile Asn Ile Phe Val Tyr Thr
20 25 30
Leu Leu Gln Ile Gly Ile Gln Ile Phe Thr Leu Phe His Gln Gly Val
35 40 45
Lys Ile Gln Arg Pro Leu His Ile Cys Gln Tyr Xaa Met Cys Tyr Tyr
50 55 60
Phe Ile Leu Glu Gln Thr Asn Met Ile Ala Leu Asn His Phe Asn Cys
65 70 75 80
Asp Phe Leu Asp Leu Val Asn Leu Lys Cys Phe Ser Cys Gly Met Phe
85 90 95
Thr Ile Leu Gly Xaa Ser Ser Leu Lys Cys Leu Val Ile Tyr Phe Pro
100 105 110
Phe Phe Ser Ile Gly Ile Ser Thr Phe Phe Pro Leu Gln Phe Lys Arg
115 120 125
Thr Met Tyr Ala Leu Gln
130

<210> 98
<211> 121
<212> PRT
<213> Homo sapiens

<220>
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<222> (5)..(5)
<223> Xaa is any amino acid

<220>
<221> misc_feature
<222> (120)..(120)
<223> Xaa is any amino acid

<400> 98

Ser Arg Glu Leu Xaa Ser Val Phe Leu Arg Ala Glu Tyr Leu His Lys
1 5 10 15
Leu Phe Glu Ile Leu His Glu Ile Phe Phe Tyr Ser Gly Pro Cys Ile
20 25 30

00131PCT1.ST25.txt

Tyr Leu Ile Ile Phe Tyr Gln Cys Gly Leu Ile Asp Thr Tyr Phe Ile
 35 40 45
 Leu Cys Ile Leu Ile Glu Tyr Tyr His Ile Leu Leu Leu Lys Leu Phe
 50 55 60
 Gln Leu Trp Pro Phe Lys Ala Leu Ser Val Ser Ser Trp Val Phe Leu
 65 70 75 80
 Thr Tyr His His His Ser Met Tyr Gly Val Cys Leu Leu Val Phe Phe
 85 90 95
 Glu Asn Phe Leu Ile Ser Trp Tyr Tyr Lys Met Leu Pro Val His Leu
 100 105 110
 Val Tyr Phe Leu Leu Gln Ser Xaa Asn
 115 120

<210> 99
 <211> 197
 <212> PRT
 <213> Homo sapiens

<400> 99

Leu Thr Trp Ser Lys Ile Ser Gln Arg Asp Phe Phe Phe Phe Phe Ile
 1 5 10 15
 Trp Gly Gln Arg Asn Gly Gly Lys Thr Pro Ser Tyr Tyr Phe Leu Pro
 20 25 30
 Glu Met Leu Phe Asn Trp Val Lys Glu Gly Asn Leu Phe Lys Pro Arg
 35 40 45
 Thr Asn Thr Met Asn Leu Gly Asn Cys Met Phe Ile Asp Leu Val Pro
 50 55 60
 Trp Ser Ile Cys Ser Leu Tyr Met Trp Ser Ile Trp Asp Phe Gln Leu
 65 70 75 80
 Lys Glu Ser Leu Glu Pro Asp Ile Ser Leu Arg Ser Leu Glu Arg Phe
 85 90 95
 Gly Leu Gln Val Leu Cys Asn Pro Trp His Ser Met Thr Phe Pro Val
 100 105 110
 His Trp Phe Lys Leu Gly Ile Val Asp Val Phe Gly Gly Glu Tyr Trp
 115 120 125
 Gln Leu Glu Cys Asn Arg Asp Thr Met Gln Ala Gly Arg Arg Tyr Val
 130 135 140
 Cys Gly Ser Gln Ala Leu Thr Pro Gln Pro Gly Val Cys Phe Ser His
 145 150 155 160
 Leu Phe Val Leu Ala Ser Gln Trp Leu Trp Asn Leu His Val Phe Leu
 165 170 175
 His Arg His Leu Leu Gly Pro Gly His Phe Leu His Ser Cys Thr Phe
 180 185 190
 Pro Leu Pro Leu Pro
 195

<210> 100
 <211> 172
 <212> PRT

00131PCT1.ST25.txt

<213> Homo sapiens

<220>

<221> misc_feature

<222> (7)..(7)

<223> Xaa is any amino acid

<220>

<221> misc_feature

<222> (22)..(22)

<223> Xaa is any amino acid

<220>

<221> misc_feature

<222> (98)..(98)

<223> Xaa is any amino acid

<400> 100

Leu Phe Leu Phe Cys Leu Xaa Phe Phe Ser Ser Lys Ile Phe Thr His
1 5 10 15

Thr Tyr Thr Cys Ile Xaa Phe Tyr Ile Asn Ser Asn Lys Cys Asp His
20 25 30

Ile Ile His Thr Ile Phe Tyr Cys Ser Ile Val Phe Trp Phe Ser Phe
35 40 45

Ser Phe Pro Ile Tyr Leu Pro Leu Asn Leu Tyr Ser Phe Leu Ile Asp
50 55 60

Thr Lys Val Ile His Thr Asn Asn Leu Leu Tyr Ile Leu Ser Tyr Phe
65 70 75 80

Tyr Ala Cys Ile His Lys Lys Thr Thr Ile His Ile Val Tyr Thr Tyr
85 90 95

Leu Xaa Cys Ile Tyr Glu Tyr Lys Tyr Thr His Arg Glu Val Leu Ser
100 105 110

Leu Ser Cys Lys Asn Leu Asn Ile His Ile Phe Leu Asn Leu Ala Phe
115 120 125

Ser Tyr Ser Thr Ile Thr Leu Ser Asn Asn Cys Val Thr Leu Tyr Ile
130 135 140

Ala Ile Cys Cys Asn Leu Phe Asn Asp Ser Pro Ile Asp Gly Gln Ser
145 150 155 160

Tyr Cys Phe Tyr Leu Phe Ser Phe Val Pro Ile Lys
165 170

<210> 101

<211> 198

<212> PRT

<213> Homo sapiens

<400> 101

Ser Cys Ile Pro Val Phe Leu Arg Leu Val Pro Phe Val Ile Ser Pro
1 5 10 15

Ser Arg Gly Pro Ser Leu His Leu Arg Trp Pro Ile Val Thr Phe Asn
20 25 30

00131PCT1.ST25.txt

Leu Pro Lys Ala Pro Cys Gln Leu Leu Pro Ala Leu His Phe Thr Ile
35 40 45
Ser Arg Ser Asn Phe Phe Val Leu Val Glu Glu Gly Cys Tyr Leu Pro
50 55 60
Val Ala Val Val Ala Lys Val Leu Phe Glu Ser Leu Pro Gly His Val
65 70 75 80
Arg Thr Trp Lys Lys Trp Phe Tyr Arg Leu Ala Val Cys Trp Cys Glu
85 90 95
Gly Trp Lys Ile Trp Trp Ser Leu Gly Lys Leu Thr Val Arg Lys Thr
100 105 110
Gln Leu Tyr Leu Leu Cys Lys His Phe Ala Gln Gln His Leu Gly Thr
115 120 125
Thr Tyr Leu Leu Ser Asn Pro Glu Leu His Pro Asn Ser Ile Pro Leu
130 135 140
Ile His Val His Phe Leu Ser Phe Tyr Lys Asp Phe Ser Asn Thr Leu
145 150 155 160
Ser Leu Leu Ile Thr Gly Gln Asn Ser Phe Tyr Asn Ser Leu Asn Gln
165 170 175
His Cys Pro Met Asp Gly Met Leu Gly Gln His Leu Asn Leu Thr Arg
180 185 190
Phe Lys Val Arg Arg Phe
195

<210> 102
<211> 233
<212> PRT
<213> Homo sapiens

<400> 102

Asn Ile Tyr Leu Phe Cys Leu Thr Cys Leu Met Thr Phe Ala Ala Leu
1 5 10 15
Val Gly Ser Ile Tyr Ser Leu Ile Ser Leu Leu Lys Met Gln Asn Arg
20 25 30
Thr Val Val Ser Met Leu Val Ala Ser Trp Ser Val Asp Asp Leu Met
35 40 45
Ser Val Leu Ser Val Thr Ile Phe Met Phe Leu Gln Trp Pro Asn Glu
50 55 60
Val Pro Gly Tyr Phe Gln Phe Leu Cys Thr Thr Ser Ala Leu Met Tyr
65 70 75 80
Leu Cys Gln Gly Leu Ser Ser Asn Leu Lys Ala Thr Leu Leu Val Ser
85 90 95
Tyr Asn Phe Tyr Thr Met His Arg Gly Val Gly Ser Gln Thr Ala Ser
100 105 110
Arg Arg Ser Gly Gln Val Leu Gly Val Val Leu Thr Val Trp Ala Ala
115 120 125
Ser Leu Leu Leu Ser Ala Leu Pro Leu Cys Gly Trp Gly Ala Phe Val
130 135 140

00131PCT1.ST25.txt

Arg Thr Pro Trp Gly Cys Leu Val Asp Cys Ser Ser Ser Tyr Val Leu
145 150 155 160

Phe Leu Ser Ile Val Tyr Ala Leu Ala Phe Gly Leu Leu Val Gly Leu
165 170 175

Ser Val Pro Leu Thr His Arg Leu Leu Cys Ser Glu Glu Pro Pro Arg
180 185 190

Leu His Ser Asn Tyr Gln Glu Ile Ser Arg Gly Ala Ser Ile Pro Gly
195 200 205

Thr Pro Pro Thr Ala Gly Arg Val Val Ser Leu Ser Pro Glu Asp Ala
210 215 220

Pro Gly Pro Ser Leu Arg Arg Ser Gly
225 230

<210> 103
<211> 219
<212> PRT
<213> Homo sapiens

<400> 103

Leu Leu Ala Leu Gly Leu Val Phe Tyr Ser Phe Gln Cys Leu Asn Val
1 5 10 15

Glu Gly His Leu Ile Pro Ser Phe His Leu Ser Phe His Ser Leu Asn
20 25 30

Ser Val Phe Leu Ala Ser Gly Glu Leu Pro Ser Leu Val Val Leu His
35 40 45

Val Tyr Cys Cys Thr Thr Ile Thr Gly Ser Met Ser Arg Gln Trp Lys
50 55 60

Leu Asn Ile Gln Asn Leu Leu Asp Ser Thr Leu Tyr Asp Met Ser Leu
65 70 75 80

Gln Leu Val Leu Ile Ser Thr Leu Ser Leu Leu Thr Val Ser Thr Met
85 90 95

Ala Phe Asn Glu Phe Cys Glu Ser Phe Ile Leu Glu Thr Glu Cys Val
100 105 110

Gln Gly Lys Pro Leu Asn Trp Gln Leu Val Ser Glu Val Arg Ile Val
115 120 125

Leu Tyr Gly Leu Phe Leu Thr Leu Gln Leu Asp Ala Asn Ser Ala Gln
130 135 140

Phe Gly Pro Glu Val Ser Cys Leu Cys Ser Leu Lys Tyr Leu Val Val
145 150 155 160

Cys Leu Thr Leu Asn Lys Phe Ala Phe Ile Lys Tyr Cys Ile Cys Tyr
165 170 175

Ser Lys Ile Thr Ile Thr Phe Phe Ser Pro Asn Asn His Trp Glu Lys
180 185 190

Pro Ala Glu Ser Cys Asn Ser Thr Glu Thr Ser Asp Pro Tyr Thr Ile
195 200 205

Tyr His Ile Ser Gly His Phe Ile Leu Pro Leu
210 215

00131PCT1.ST25.txt

<210> 104
 <211> 179
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (176)..(176)
 <223> Xaa is any amino acid

<400> 104

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Leu Thr Gly Ile Pro Phe Tyr Trp Trp Leu Asp Met Trp Arg Asp Thr
1          5          10          15
Asp Ser Pro Arg Thr Leu Asp Glu Val Leu Lys Trp Ala His Cys Leu
20          25          30
Thr Val Tyr Phe Ile Pro Cys Gly Val Phe Leu Val Thr Asn Ser Ala
35          40          45
Ile Ile His Arg Leu Arg Arg Arg Gly Arg Ser Gly Leu Gln Pro Arg
50          55          60
Val Gly Lys Ser Thr Ala Ile Leu Leu Gly Ile Thr Thr Leu Phe Thr
65          70          75          80
Leu Leu Trp Ala Pro Arg Val Phe Val Met Leu Tyr His Met Tyr Val
85          90          95
Ala Pro Val His Arg Asp Trp Arg Val His Leu Ala Leu Asp Val Ala
100         105         110
Asn Met Val Ala Met Leu His Thr Ala Ala Asn Phe Gly Leu Tyr Cys
115         120         125
Phe Val Ser Lys Thr Phe Arg Ala Thr Val Arg Gln Val Ile His Asp
130         135         140
Ala Tyr Leu Pro Cys Thr Leu Ala Ser Gln Pro Glu Gly Met Ala Ala
145         150         155         160
Lys Pro Val Met Glu Pro Pro Gly Leu Pro Thr Gly Ala Glu Val Xaa
165         170         175

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Arg Arg Gly

<210> 105
 <211> 222
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (188)..(188)
 <223> Xaa is any amino acid

<400> 105

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Arg Arg Val Lys Ser Val Ile Leu Val Met Leu Leu Gly Pro Leu Leu
1          5          10          15
Phe Leu Ala Cys Gln Leu Phe Val Ile Asn Met Lys Glu Ile Val Arg
56

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00131PCT1.ST25.txt

20 25 30
 Thr Lys Glu Tyr Glu Gly Asn Met Thr Trp Lys Ile Lys Leu Arg Ser
 35 40 45
 Ala Val Tyr Leu Ser Asp Ala Thr Val Thr Thr Leu Gly Asn Leu Val
 50 55 60
 Pro Phe Thr Leu Thr Leu Leu Cys Phe Leu Leu Leu Ile Cys Ser Leu
 65 70 75 80
 Cys Lys His Leu Lys Lys Met Gln Leu His Gly Lys Gly Ser Gln Asp
 85 90 95
 Pro Ser Thr Lys Val His Ile Lys Ala Leu Gln Thr Val Ile Phe Phe
 100 105 110
 Leu Leu Leu Cys Ala Val Tyr Phe Leu Ser Ile Met Ile Ser Val Trp
 115 120 125
 Ser Phe Gly Ser Leu Glu Asn Lys Pro Val Phe Met Phe Cys Lys Ala
 130 135 140
 Ile Arg Phe Ser Tyr Pro Ser Ile His Pro Phe Ile Leu Ile Trp Gly
 145 150 155 160
 Asn Lys Lys Leu Lys Gln Thr Phe Leu Ser Val Leu Arg Gln Val Arg
 165 170 175
 Tyr Trp Val Lys Gly Glu Lys Pro Ser Ser Pro Xaa Ile His Glu Arg
 180 185 190
 Gly Ile Val Cys Leu Leu Ala Glu Asn Lys Leu Val Val Tyr Glu Thr
 195 200 205
 Phe Tyr Ile Ser Tyr Trp Phe Phe Tyr Thr Val Cys Val Glu
 210 215 220

<210> 106
 <211> 172
 <212> PRT
 <213> Homo sapiens

<400> 106

Gly Phe Leu Ala Gln Glu Arg His His Phe Leu Tyr Val Ala Phe Leu
 1 5 10 15
 Cys Ser Gln Cys Asp Lys Ser Glu Asn Phe Cys Leu Asn Lys Leu Leu
 20 25 30
 Trp Leu Phe Asp Ser Glu Leu Cys Lys Ser Leu Ala Asn Ala Asn Pro
 35 40 45
 Leu Ile Leu Leu Gly Ala Val Thr Gly Tyr Phe Ser Pro Ala Leu Phe
 50 55 60
 Tyr Pro Ser Leu Asp Lys Thr Thr His Thr His Thr His Thr
 65 70 75 80
 His Thr His Met His Thr Leu Phe Leu Ser Cys Lys Phe Lys Ser Leu
 85 90 95
 Arg Gln Ser Arg Lys Val Asp Ser Lys Phe Asn Pro Gln Asp Ser Arg
 100 105 110
 Thr Lys Gln Phe Cys Phe Lys Arg Glu Asn Ile Thr Asp Leu Glu Cys
 57

00131PCT1.ST25.txt

115 120 125
 Gln Ser Tyr Ile Gln Thr Leu Glu Asn Cys Ala Asn Val Ser Asn Ile
 130 135 140
 Ala Lys Ile Ala Asn Ser Phe Arg His Ser Asp Leu Ser Lys Phe Tyr
 145 150 155 160
 Lys Asn Thr Tyr Phe Asn Lys Phe Arg Ala Asn Lys
 165 170

<210> 107
 <211> 107
 <212> PRT
 <213> Homo sapiens

<400> 107

Gly Trp Gly Pro Gly Arg Ala Trp Val Gly Val Leu Val Cys Leu Val
 1 5 10 15
 Tyr Asn Thr Ser Ser Cys Ser Ser Met Pro Gly Gln Arg Val Cys Pro
 20 25 30
 Cys Thr Cys Ile Leu Ile Cys Gly Gln Gly Ser Val His Ala Gly Ala
 35 40 45
 Trp Arg Cys Gly Phe Thr His Thr Phe Pro Gly Ser Gln Gly Trp Lys
 50 55 60
 Gly Leu Trp Lys Arg Pro Ser Pro Ser Ser Leu Thr Cys Ser Ala Ile
 65 70 75 80
 Ser Met Pro Asn Ala His Leu Asp Ser Ala Ser Leu Pro Val Thr Gly
 85 90 95
 Ser Ser Leu Leu Pro Gln Ala Ala His Leu Cys
 100 105

<210> 108
 <211> 95
 <212> PRT
 <213> Homo sapiens

<400> 108

Asp Ser Ser Pro Arg Ser Phe Leu Ser Thr Gly Gly Thr Trp Asp Ala
 1 5 10 15
 Val Asn Cys Ser Trp Asp Thr Phe Ser Leu Gly Pro Phe Ala Phe Pro
 20 25 30
 Val Arg Ser Thr Leu Arg Met Pro Ser Tyr Ser Leu Val Thr Ile Ser
 35 40 45
 Gly Gly Arg Ala Ser Pro Thr Trp Phe Cys Arg Gly Gln Ala Glu Lys
 50 55 60
 Tyr Gly Thr Val His Lys Leu Asn Leu Val Thr Arg Ser Tyr Tyr Phe
 65 70 75 80
 Arg Gln Ile Glu Arg Lys Arg Gly Pro Trp Glu Val Phe Val Phe
 85 90 95

<210> 109
 <211> 87
 <212> PRT

00131PCT1.ST25.txt

<213> Homo sapiens

<220>

<221> misc_feature

<222> (26)..(26)

<223> Xaa is any amino acid

<400> 109

Leu Leu Phe Leu Val Ile Tyr Phe His Ile Ile Lys Lys Tyr Thr Lys
1 5 10 15

Cys Cys Tyr Phe Leu Ile Tyr Gln Phe Xaa Ile Ile Phe Ile Phe Cys
20 25 30

His Asp Ile Trp Val Tyr Thr Cys Phe Leu Val Leu Tyr Gly Leu Ser
35 40 45

Ile Val Ile Ala Pro Ser Cys Ser Ser Ala Leu Val Ile Phe Leu Leu
50 55 60

Ser Phe Thr Ile Tyr Ser Val Phe Ser Leu Glu Ser Val Phe Phe Phe
65 70 75 80

Phe Phe Arg Asn Trp His Ser
85

<210> 110

<211> 118

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<222> (81)..(81)

<223> Xaa is any amino acid

<400> 110

Phe Leu Leu Val Ile Ile Leu Gly Met Tyr Pro Trp Ala Asp Ile Gly
1 5 10 15

His Leu Arg Ser Met Ile Ser Leu Tyr Leu His Tyr Asn Leu Cys Ile
20 25 30

Val Ile Val Cys Gly Leu His Leu Leu Val Cys Ile Arg Leu Leu Phe
35 40 45

Asp Met Phe Cys Leu Ser Val Leu Gln Val Ala Lys Asn Tyr Leu Phe
50 55 60

Trp Val Asn Ser Phe Thr Thr Gly Leu Tyr Ser Pro Cys Leu Lys Pro
65 70 75 80

Xaa His Cys Leu Met Arg Phe Pro Asn Ile Val Arg Leu Ala Asp Trp
85 90 95

Arg Val Leu Ser Phe Gln Cys Met Glu Ala Pro Gly Ser Asn Pro Val
100 105 110

Leu Ile Phe Cys Leu Leu
115

<210> 111

<211> 98

00131PCT1.ST25.txt

<212> PRT
 <213> Homo sapiens

<400> 111

Arg Val Thr Ala Gly Gly Glu Arg Leu Asn Leu Met Val Ser Trp Asp
 1 5 10 15
 Ser Ser Ile His Ala Ala Cys Ala Asn Arg Gly Ile Phe Lys Leu Phe
 20 25 30
 Ile Gly Phe Ser Leu Pro His Leu Lys Asn Lys Val Val Phe Glu Met
 35 40 45
 Asp Trp Lys Lys Lys Phe Ala Tyr Ile Ser Gln Lys Trp Ile Phe Thr
 50 55 60
 Gly Gly Asn Val Cys Ser Tyr Leu Gly Val Asp Leu Cys His Gly Arg
 65 70 75 80
 Pro Leu Ala Ser Pro Trp Glu Thr Val Ser Glu His Lys Thr Ser Pro
 85 90 95
 Val Leu

<210> 112
 <211> 116
 <212> PRT
 <213> Homo sapiens

<400> 112

Trp Pro Leu Arg Thr Gly Ile Tyr Gly Ser Ser Ile Val Pro Asp Gln
 1 5 10 15
 Gly Asn Leu Ile Phe Leu Pro Thr Thr Ser Lys Val Thr Phe Arg Gln
 20 25 30
 Gly Arg Gln Gly Pro Gly Leu Gly Glu Leu Cys Leu Val Trp Cys Arg
 35 40 45
 Leu Val Ser Ser Pro Arg Leu Gln Val Trp Val Gln Ala Pro Pro Phe
 50 55 60
 Leu Phe Pro Ala Thr Ser Leu Gly Pro Trp Ser Ala Pro Ile Ala Pro
 65 70 75 80
 Gly Leu Gly Glu Val Leu Gly Ala Leu Trp Gln Pro Ser Leu Val Ser
 85 90 95
 Val Thr Pro Ala Ser Pro Ala Leu Thr Trp Pro Arg Pro Pro Leu Asp
 100 105 110
 Glu Glu Gly Arg
 115

<210> 113
 <211> 77
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (68)..(68)
 <223> Xaa is any amino acid

00131PCT1.ST25.txt

<400> 113

Tyr Ser Trp Ile Cys Val Leu Val Leu Leu Leu Ile Leu Glu Asn Ser
1 5 10 15

Trp Pro Leu Leu Leu Gln Ile Phe Leu Leu Ser Tyr Tyr Ser Asn Gln
20 25 30

Thr Cys Ile Pro Val Phe Glu Ile Phe Pro Tyr Ser Trp Phe Tyr Ser
35 40 45

Val Phe Leu Ser Val Cys Leu Phe Val His Ser Phe Phe Ser Leu His
50 55 60

Phe Ser Phe Xaa Phe Phe Leu Ser His Leu Lys Thr His
65 70 75

<210> 114

<211> 115

<212> PRT

<213> Homo sapiens

<400> 114

Arg Val Lys Arg Arg Gln Gln Pro Pro Arg Gly Lys Gly His Ile Ser
1 5 10 15

Trp Ser Ser Leu Pro Asn Ser Ser Trp Glu Pro Pro Tyr Phe Leu Arg
20 25 30

Gly Gly Gly Arg Gln Pro Arg Met Arg Leu Ala Asn Phe Gly Gly Tyr
35 40 45

Leu Val Ala Glu Leu Pro Gly Ser Gly Phe Ser Pro Pro Arg His Ile
50 55 60

Val Leu Val Pro Gly Leu Tyr Arg Ile Asn Glu Cys Ser Gln Gln Gln
65 70 75 80

Gly Arg Ala Ser Pro Ala Leu Pro Gly Pro Pro Gly Val Ser Ser Leu
85 90 95

Pro Trp Leu Gln Glu Lys Glu Lys Leu Ser Ile Thr Lys Ile Ser Met
100 105 110

Gly Lys Ala
115

<210> 115

<211> 102

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<222> (61)..(61)

<223> Xaa is any amino acid

<400> 115

Arg His Arg Lys Arg Lys Arg Gly Ser Asp Phe Gly Arg Gly His Thr
1 5 10 15

Ser Glu Gln Gly Ile Val Phe Ser Glu Arg Gln Arg Arg Tyr His Thr
20 25 30

00131PCT1.ST25.txt

His Thr His Ile Ser Phe Pro Phe Leu Cys Ser Leu Leu Val Ser Phe
 35 40 45
 Val Ala Phe Leu Leu Cys Ser Leu Pro Cys Leu Val Xaa Trp Ala Tyr
 50 55 60
 Lys Val Gly Leu Arg Leu Pro Tyr Ser Gly Ile Trp Phe Ile Thr Asn
 65 70 75 80
 Lys Leu Glu Ser Phe Val Asp Lys Asp Gly Trp Thr Asp Lys Gly Lys
 85 90 95
 Ser Pro Thr Gln Lys Pro
 100

<210> 116
 <211> 103
 <212> PRT
 <213> Homo sapiens

<400> 116

Arg Phe Gly Ser Arg Leu Tyr Gln Leu Val Gln Ile Ile Ile Phe Leu
 1 5 10 15
 Phe Leu Thr Pro Cys Arg Gln Thr Ala Ala Arg Met Arg Asp Pro Arg
 20 25 30
 Ala Pro Gly Ala Pro Ile Cys Ser Ala Glu Gln Cys Val Val His Pro
 35 40 45
 Leu Ser Lys Leu Gln Arg Gly Arg Ala Asp Gly Ala Thr Leu Pro Ser
 50 55 60
 Lys Leu Gln Gln Lys His Ile Cys Pro Pro Gly Gln Val Leu Asp Pro
 65 70 75 80
 Ser Thr Ile His Ile Phe Ser Trp Ile Ala Phe Arg Arg Arg Arg Leu
 85 90 95
 Ser Cys Ser Trp Trp Val Val
 100

<210> 117
 <211> 81
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (29)..(29)
 <223> Xaa is any amino acid

<400> 117

Glu Ala Phe Pro Gly Ser Phe Ser Val Cys Thr Pro Ile Leu Thr Thr
 1 5 10 15
 Gly Leu Leu Asn Val Leu Asn Ser Val Trp Val Tyr Xaa Arg Glu Lys
 20 25 30
 Lys Arg Ile Asn Ser Leu Leu Val Gln Trp Tyr Phe Lys Phe Trp Ser
 35 40 45
 Pro Phe Pro Val Cys Leu Leu Leu Met Thr Phe Gln His Leu Gln Ile
 62

00131PCT1.ST25.txt
60

50

55

Leu Leu His Thr Phe Phe Pro Ser Leu Lys Ala Ala Phe Ser Gly Arg
65 70 75 80

Glu

<210> 118
<211> 90
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<222> (74)..(74)
<223> Xaa is any amino acid

<400> 118

Cys Ala Gln Gly Ala Cys Thr Trp Ser Cys Ser Thr Phe Ile Tyr Leu
1 5 10 15
Pro Leu Phe Leu Leu Ser Val Asn Ile Leu Lys Lys Ser Leu Ile Ser
20 25 30
Gly Arg Ile Arg Pro Glu Lys Lys Lys Lys Ala Trp Cys Ser Ser Gln
35 40 45
Thr Cys His Met Asp Phe Tyr Asn Ser Phe Leu Thr Cys Ser Lys Val
50 55 60
Ser Glu Lys Arg Ser Glu Asp Ser Ser Xaa Met Gln Arg Thr Gly His
65 70 75 80
Met His Leu Pro Leu Leu Leu Glu Ile Met
85 90

<210> 119
<211> 109
<212> PRT
<213> Homo sapiens

<400> 119

Phe Arg Gly Ser Ser Phe Leu Leu Phe Phe Phe Ser Arg Met Ala Leu
1 5 10 15
Thr Thr Tyr His Thr Val Thr Ile Pro Lys Arg Cys Phe Leu Ala Thr
20 25 30
Val Leu Val Gly Trp Phe Pro Val Val Ser Lys Gly Lys Tyr Thr Gly
35 40 45
Pro Gly Thr Trp Val Glu His Phe Val Phe Leu Tyr Phe Leu Met Gly
50 55 60
Lys Asn Val Ser Ser Gly Ser Ser Phe Phe Phe Phe Ser Glu Thr Glu
65 70 75 80
Phe Ser Gln Pro Met Leu Trp Glu His Ile Pro Gly Gly Ser Ser Tyr
85 90 95
Ser Gln Ala Ser Gln Val Val Ile Phe Ile Arg Lys Asn
100 105

00131PCT1.ST25.txt

<210> 120
<211> 79
<212> PRT
<213> Homo sapiens

<400> 120

Val Phe Thr Phe Val Arg Pro Arg Pro Phe Asp Val Leu Leu Leu Val
1 5 10 15
Gln Lys Cys Asp Ser Cys His Cys Asn Gln Phe Leu Ser Leu Ala Asn
20 25 30
Trp Pro Pro Tyr Gln Val Asn Cys Pro Leu Val Ile Pro Leu Glu Pro
35 40 45
Leu Leu Leu Asp Phe Ile Val Phe Cys Lys Ile Thr Phe Tyr Ser His
50 55 60
Val Ile Cys Lys Leu Arg Met Val Leu Gly Asn Pro Thr Ala Leu
65 70 75

<210> 121
<211> 44
<212> PRT
<213> Homo sapiens

<400> 121

Leu Leu Pro Phe His Leu His Leu Phe His His Cys Asp Asp Leu Leu
1 5 10 15
Tyr Phe Thr Gly Leu Ser Met Leu Gly Ser Ile Ser Thr Lys His Cys
20 25 30
Leu Ser Ile Pro Val Ala His Pro Ser Thr Ala Ala
35 40

<210> 122
<211> 96
<212> PRT
<213> Homo sapiens

<400> 122

Glu Asp Arg Gln Glu Arg Asp Thr Gly Ser Phe Cys Arg Asp Asp Asn
1 5 10 15
Ser Ser Pro Leu Lys Gly Thr Val Ile Pro Lys Gly Thr Thr Asn Pro
20 25 30
Lys Ala Ser Val Pro Met Arg Leu Trp Leu Leu Leu Trp His Pro Trp
35 40 45
Val Lys Thr Trp Pro Gln Leu Ala Trp Arg Leu Ser Val Asn Ser Cys
50 55 60
Tyr Thr Ser Ser Phe Pro Cys Ser Leu Asn Ser Pro Gly Asn Phe His
65 70 75 80
Ala Leu Val Gln Val His Lys Ser Val Phe Glu Ser Ile Ser Glu Pro
85 90 95

<210> 123
<211> 137
<212> PRT
<213> Homo sapiens

00131PCT1.ST25.txt

<220>
 <221> misc_feature
 <222> (6)..(6)
 <223> Xaa is any amino acid

<220>
 <221> misc_feature
 <222> (61)..(61)
 <223> Xaa is any amino acid

<400> 123

Gln Phe Gly Trp Ile Xaa Lys Ser Trp Ile Thr Tyr Tyr Phe Pro Gly
 1 5 10 15
 Phe Phe Val Ser Tyr Phe Cys Leu Pro Ala Ser Asn Ile Val Val Asn
 20 25 30
 Tyr Lys Val Ser Leu Ile Phe Leu Leu Cys Ile Lys Tyr Gly Lys Glu
 35 40 45
 Thr Asn Thr Val Thr Lys Tyr Lys Asn Thr Val Ser Xaa Leu Arg Phe
 50 55 60
 Asn Leu Val Ser Leu Ser Cys Ile Ser Leu Ala Gly Leu Ser Tyr Gln
 65 70 75 80
 Ser Asn Cys Cys Ala Arg Ser Pro Arg Glu Pro Phe Leu Pro Cys Cys
 85 90 95
 Cys Ser Thr Ile Pro Phe Trp Ala Phe Cys His Pro Gln Asn Gln Lys
 100 105 110
 Trp Asp Val Gly Lys Ser Thr Phe Gln Leu Ala Lys Glu Glu Lys Arg
 115 120 125
 Gln Asn Thr Glu Lys Ala Asp Phe Leu
 130 135

<210> 124
 <211> 73
 <212> PRT
 <213> Homo sapiens

<400> 124

Asn Trp Pro Arg Val Gly Leu Gly His Gly Ser Leu Phe Lys Ala Pro
 1 5 10 15
 Glu Gln Cys Trp His Pro Phe Met Val Val Arg His Trp Gly Ser Ser
 20 25 30
 Phe Gly His Leu Val Gly Thr Glu His Lys Ala Pro Pro Ile Ser Gln
 35 40 45
 Leu Leu Ala Lys Glu Asn Glu Thr Val Pro Ser Gln Ile Phe Phe Phe
 50 55 60
 Lys Leu Leu Ser Arg Gln Arg Arg Arg
 65 70

<210> 125
 <211> 128
 <212> PRT

00131PCT1.ST25.txt

<213> Homo sapiens

<400> 125

Phe Met Ile Ser Ser Arg Met Pro Cys Leu Leu Val Leu Asn Ser Val
1 5 10 15

Ser Phe Pro Leu Phe Leu Ala Val Tyr Tyr Trp Pro Ala Ser Leu Asp
20 25 30

Gly Ala Ala Gly Met Val Gln Ile Asn Glu Gly His Thr Lys Val Ile
35 40 45

Leu Leu Lys Ala His Val Gly Leu Arg Pro Glu Leu Thr Asp Thr Glu
50 55 60

Met Ser Leu Ile Leu Cys Leu Phe His Cys Leu Trp Tyr Tyr Ser Ala
65 70 75 80

Phe Thr Glu Glu Arg Val Leu Gly Asn Arg Asn Thr Arg Ile Ile Leu
85 90 95

Val Gln Gln Leu Leu Ala Thr Pro Lys Phe Thr Tyr Phe Leu Pro Pro
100 105 110

Ala Phe Phe Ile Asp Leu Ala Ala Ser Glu Ile Phe Ala Ala Ser Gln
115 120 125

<210> 126

<211> 98

<212> PRT

<213> Homo sapiens

<400> 126

Pro Pro Ala Asn Gly Lys Ser Tyr Ile Tyr Arg Lys Tyr Ile Leu Cys
1 5 10 15

Ile Pro Leu Asp Val Phe Ser Pro Phe Thr His Ala Ser Leu Leu Glu
20 25 30

Phe His Ile Pro Asp Phe Leu Thr Val Ala Leu His Asp His Glu Thr
35 40 45

Phe Val His Pro Ser Ile Pro Ile Ser Phe Lys Tyr Ser Leu Lys Phe
50 55 60

Ile Lys Ala Thr Ser Leu Thr Val Val Leu Asp Phe Pro Leu Ser Ser
65 70 75 80

Leu Ile Cys Lys Ser Leu Thr Leu Val Ile Leu Val Thr Leu Lys Trp
85 90 95

Cys Leu

<210> 127

<211> 91

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<222> (77)..(77)

<223> Xaa is any amino acid

00131PCT1.ST25.txt

<400> 127

Phe Phe Met Ser Leu Ala Thr Leu Phe Asn Phe Phe Lys Val Ala Ser
 1 5 10 15
 Leu Phe Phe Leu Met Asn Gly Pro Cys Phe Met Phe Val Ala Ile Phe
 20 25 30
 Met Val Ser Arg Leu Gly Lys Leu Leu Phe Leu Phe Leu Trp Tyr His
 35 40 45
 Ser Ser Ser Pro Tyr Cys Ser Ala Val Val Ser His Asn Lys Leu Ser
 50 55 60
 Gly Ala Arg Gly Val Thr Tyr Arg Lys Gln Gly Ala Xaa Leu Ala Pro
 65 70 75 80
 Met Lys Leu Glu Met Ala His Gly Glu Gly Arg
 85 90

<210> 128

<211> 126

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<222> (25)..(25)

<223> Xaa is any amino acid

<220>

<221> misc_feature

<222> (115)..(115)

<223> Xaa is any amino acid

<400> 128

Phe Asn Asn Phe Tyr Lys Ser Gln Thr Leu Tyr Leu His Ile Tyr Ser
 1 5 10 15
 Phe Ser Leu Leu Lys Phe Gln Ile Xaa Leu His His Leu Lys Cys Ile
 20 25 30
 Phe His Gly Phe Val Phe Phe Leu Thr Phe Asn Phe Ile Leu Leu Gln
 35 40 45
 Leu Ser Thr Phe His Trp Ser Ile Arg Gln Cys Pro Cys Phe Leu Asn
 50 55 60
 Cys Val Asp Leu Arg Val Asn Ser Lys Ala Phe Phe Ile Leu Phe Thr
 65 70 75 80
 Val Phe Thr Phe Ile Ser Tyr Ser Cys Pro Ser Tyr Tyr Pro Arg Val
 85 90 95
 Ser Ala Asp Ser Ser His Phe Phe Met His Val Val His Leu His Cys
 100 105 110
 Asn Ile Xaa His Lys Asn Tyr Ile Tyr Ile Glu Ser Pro Val
 115 120 125

<210> 129

<211> 109

<212> PRT

<213> Homo sapiens

00131PCT1.ST25.txt

<220>
 <221> misc_feature
 <222> (85)..(85)
 <223> Xaa is any amino acid

<400> 129

Pro Cys Asp Val Gln Met Gln Ile Thr Thr Cys Ile Leu Ser Ala Arg
 1 5 10 15
 Ser Val Phe His Ile Met Glu Val His Ser Ile Thr Thr Met Lys Ser
 20 25 30
 Lys Gln Val His Tyr Tyr His Leu Pro Phe Trp Lys Ser Ile Leu Arg
 35 40 45
 Ile His Pro Glu Ile Pro Ser Leu Phe Leu Gln Arg Ile Val Tyr Ser
 50 55 60
 Ala Ser His Trp Leu Arg Phe Gly Phe Trp Phe Cys Leu Pro Leu Ser
 65 70 75 80
 Phe Glu Ser Cys Xaa Met Phe Leu Ile Val Ile Gln Ile Phe Leu Thr
 85 90 95
 Asn Pro Ala Glu Gln Gln Gln His Leu Lys Leu Arg Arg
 100 105

<210> 130
 <211> 102
 <212> PRT
 <213> Homo sapiens

<400> 130

Ile Ser His His Thr Glu Asn Pro Thr Met His Ser Val Glu Ser Leu
 1 5 10 15
 Phe Lys Thr Asp Pro Lys Ser Asn Ser Pro Asn Leu Cys Pro Ala Ala
 20 25 30
 Leu Val Tyr Ala Thr Gly Gly Leu Ser His Pro Ala Leu Leu Thr Gly
 35 40 45
 Phe Leu Leu Arg Ala Pro Ala Tyr Phe Leu Ala His Leu Arg Thr Gly
 50 55 60
 Thr Gln Val Asn Leu Phe Arg Ser Asn Leu Gly Asn Ala Ser Leu Leu
 65 70 75 80
 Leu Arg Thr Leu Pro Tyr Leu Leu Ile Ser Ala Arg Val Thr Ser His
 85 90 95
 Ser Pro His Cys Gln Lys
 100

<210> 131
 <211> 113
 <212> PRT
 <213> Homo sapiens

<400> 131

Gln Ser Gln Ile Leu Val Ile Thr His Ser Glu Gly Leu Ser Val Pro
 1 5 10 15

Phe	Arg	Asn	Val	Asp	Asn	Gln	Glu	Leu	Ala	Glu	Phe	Ser	Thr	Arg	Ala
			20					25					30		
Ile	Cys	Gly	Ser	Tyr	Gln	Gly	Gln	Val	Ala	Asn	Phe	Thr	Trp	Leu	Ile
		35					40					45			
Ala	Trp	Asp	Val	Phe	Leu	Lys	Asp	Val	Pro	Arg	Ile	Lys	Asp	Ser	Pro
	50					55					60				
Ser	Val	Ala	Pro	Phe	Phe	Ser	Trp	Leu	Asn	Leu	Thr	Gly	Lys	Ala	Leu
65					70					75					80
Gly	Val	Gly	Arg	Gly	Gly	Leu	Trp	Val	Phe	Ile	Asp	Glu	Phe	Cys	Lys
				85					90					95	
Ala	Ser	Leu	Val	Asp	Leu	Ser	Tyr	Met	Ala	Trp	Asp	Phe	Ser	Ile	Ser
			100					105					110		

<210>	132
<211>	104
<212>	PRT
<213>	Homo sapiens

[illegible]

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<210> 133
<211> 115
<212> PRT
<213> Homo sapiens
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[illegible]

50

55

60

Gln Leu Leu Ser Ser Ser Arg Phe Leu Trp Ser Ser Arg Asn Ile His
65 70 75 80

Leu Ser Asp Leu Tyr Gly Pro Gln Ile His Arg Ala Thr Ile Phe Ile
85 90 95

Thr Thr Ala Gly Ser Cys Leu Pro Phe Leu Phe Glu Gln Lys Thr Leu
100 105 110

Phe Ser Ile
115

<210>	134
<211>	171
<212>	PRT
<213>	Homo sapiens

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<220>
<221> misc_feature
<222> (22)..(22)
<223> Xaa is any amino acid
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<400> 134

Phe Ala Val Phe Leu Ser Leu Cys Ser Ser Lys Leu Phe Pro Val Ile
1 5 10 15

Cys His Trp Ile Cys Xaa Ser Phe Leu Leu Leu Gly Leu Val Cys Cys
20 25 30

Gly Thr Ser Leu Val Asn Phe Ser Val Tyr Val Val Gln Pro Met Ile
35 40 45

Ser Val Trp Tyr Phe Leu Arg Phe Pro Ile Ser Leu Leu Lys Phe Ser
50 55 60

Leu Tyr Phe Cys Val Leu Asp Glu His Leu Val Ile Ile Phe Asn Tyr
65 70 75 80

Leu Leu Asp Lys Ser Cys Lys Val Gly Phe Cys Met Phe Ile Leu Phe
85 90 95

Leu Cys Leu Glu His Phe Tyr Leu Ile Leu His Phe Phe Leu Thr Leu
100 105 110

Tyr Val Gly Phe Cys Ile Leu Thr Lys Gln Ala Pro Leu Pro Val Phe
115 120 125

Met Asp Trp Phe Tyr Lys Arg Glu His Phe His Gln Gln Ile Gln Pro
130 135 140

Lys Ile Met Val Ala Tyr Asn Asn Ser Phe Pro Pro Glu Glu Glu Leu
145 150 155 160

Gly Ser Cys Asp Phe Cys Pro Phe Ile Leu Cys
165 170

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<210> 135
<211> 203
<212> PRT
<213> Homo sapiens
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<400> 135

00131PCT1.ST25.txt

Ser Gly Trp His Arg Ile Ser Gly Glu Asn Cys Gly Glu Tyr Gly Glu
1 5 10 15

Asn Lys Lys Arg Arg Lys Arg Ser Lys Ser Thr Trp Gly Arg Arg Arg
20 25 30

Asn Ile Thr Asn Arg Glu Trp His Ile Leu Lys Gln Gly His Glu Ser
35 40 45

Cys Leu Gln Ser Ser Glu Arg Lys Trp Phe Lys Gln Phe Met Phe Glu
50 55 60

Ser Leu Ser Leu Asn Ile Pro Trp Leu Phe Leu Gly Ser Met Glu Asn
65 70 75 80

Val Ser Ala Leu Ser Leu Leu Thr Val Glu Ser Pro Thr Ser Met Phe
85 90 95

Asp Tyr Cys Asp Asp Ser Leu Glu Arg Val Lys Ser Ala Leu Asp Ile
100 105 110

Phe Ser Met Ile Ile Tyr Thr Val Thr Phe Phe Leu Gly Leu Ala Gly
115 120 125

Asn Gly Leu Val Ile Trp Val Val Gly Phe His Met Ser Cys Thr Val
130 135 140

Asn Thr Val Trp Val Val Pro Gln Pro Ala Arg Gly Leu His His His
145 150 155 160

Leu Pro Thr Ala Ser Pro Ala Gly Tyr Gly Ser Ser Val Thr Leu Trp
165 170 175

Pro Ala Ala Leu Thr Gln His His Val Tyr Phe Leu Ser Gly Gln Cys
180 185 190

Leu Pro Ser Asp Pro His Leu His Gly Pro Leu
195 200

<210> 136
<211> 94
<212> PRT
<213> Homo sapiens

<400> 136

Pro Gly Pro Ala Gly Arg Lys Cys Ser His Phe Leu Trp Leu Leu Gly
1 5 10 15

Phe Arg Met His Arg Asn Thr Phe Ser Leu Tyr Thr Leu Asn Leu Ala
20 25 30

Gly Ala Asp Phe Phe Leu Cys Ser Gln Ile Leu Glu Ile Val Asn Phe
35 40 45

Tyr His Asp Phe Phe Leu Ser Ile Ser Thr Tyr Phe Thr Thr Val Met
50 55 60

Thr Phe Ser Thr Leu Gln Ala Ala Cys Trp Ala Pro Ser Ala Pro Ser
65 70 75 80

Thr Ala Cys Pro Ser Leu Trp Pro Ile Leu Val Pro Leu Pro
85 90

<210> 137
<211> 9
<212> PRT

00131PCT1.ST25.txt

<213> Artificial Sequence

<220>

<221> misc_feature

<223> Substrate Peptide

<400> 137

Ala Pro Arg Thr Pro Gly Gly Arg Arg
1 5

